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LIVER FUNCTION AND OTHER BLOOD CHEMISTRY TESTS IN MULTIPLE SCLEROSIS

NORMAN B. DOBIN, M.D.
AND
JOHN L. SWITZER, M.D.
CHICAGO

DEMYELINATING lesions in the central nervous system have been known to develop in the course of, and particularly in the terminal metabolic derangements of, such disorders as hepatic diseases, uremia, eclampsia, and porphyria. The development of demyelinating lesions of the central nervous system in disorders other than the nervous system has been investigated by various workers with respect to clues for the pathogenesis of the demyelinating lesions of multiple sclerosis.

The present study deals with the measurement, quantitative and qualitative, of various substances in the blood and urine often used to discover disordered liver function. Although the tests may be used as a battery to assess liver function, they are also useful in comparing the results with those in normal man and with reports of other investigators studying functions other than those of the liver. None of the patients included in this study had clinical symptoms or signs suggesting liver disease.

The diagnosis of multiple sclerosis in the patients examined in this study was established by members of the neurological staff of the Department of Nervous and Mental Diseases of Northwestern University Medical School and included private patients of these physicians, as well as other patients examined by them at the Veterans Administration Hospital, Hines, Ill., and at the Cook County Hospital. The chemical analysis of the blood and urine samples collected from these patients was conducted under the supervision of Dr. Hans Popper and his staff at the Hektoen Institute for Medical Research of the Cook County Hospital.

MATERIAL

Fifty-eight patients with multiple sclerosis were each examined for evidence of liver dysfunction by a battery of 27 chemical hepatic function tests, which were useful for other studies as well. Fourteen of this group of patients were in the acute or active phase, and 44 patients, in the chronic, inactive, or slowly progressive phase of the disorder. There were 13 males and 45 female patients; their ages ranged from 18 to 64 years.

This work has been aided by a grant from the Multiple Sclerosis Foundation of America, Chicago; Dr. Lewis J. Pollock, responsible investigator.

From the Department of Nervous and Mental Diseases and the Department of Pathology, Northwestern University Medical School, and the Hektoen Institute for Medical Research, Cook County Hospital.

METHODS

Laboratory Tests.—First morning urine specimens and fasting blood samples were submitted for study immediately after collection of the specimens. In the course of the laboratory studies, if an abnormality was detected, at least one more determination was conducted from the same specimen and, on occasion, on another sample obtained from the same patient. With respect to the sulfobromophthalein sodium U.S.P. (Bromsulphalein sodium) test, 5 mg. of the drug per kilogram of body weight was administered intravenously in one arm, and blood samples were obtained from the other arm after a 45-minute interval.

The hepatic tests were, for convenience, divided into several categories: (*a*) lipid studies, including phenol turbidity,[1] total lipid turbidity,* total cholesterol, free cholesterol,† cholesterol esters,† ratio of free cholesterol to total cholesterol,† ratio of cholesterol esters to total cholesterol,† and lipid phosphorus[2]; (*b*) enzyme studies, including serum esterase,[3] alkaline phosphatase,[4] and, coincidentally, serum inorganic phosphorus[5]; (*c*) bilirubin excretion in the blood by the total van den Bergh test,[6] and in the urine by urinary bilirubin[7]; (*d*) obstructive mechanisms by urinary urobilinogen[8]; (*e*) detoxifying and dye excretion ability, measured by the sulfobromophthalein retention[9]; and (*f*) plasma proteins determinations, including total protein, true albumin, true globulin, true albumin-globulin ratio,[10] Howe albumin, Howe globulin, Howe albumin-globulin ratio,[11] gamma globulin,[12] mucoprotein,[13] cephalin flocculation,[14] thymol turbidity,‡ and zinc sulfate turbidity.§

The tests used and the limits of normality accepted in the study are given in Table 1. The selected range of values was chosen because it represented unequivocally normal values. The total serum proteins were fractionated into albumin and globulin by the older Howe[11] method and also by a more recent method, which more closely mirrored electrophoretic results. Gamma globulin was determined turbidimetrically.

Statistical Procedure.—The material was analyzed statistically for group mean and standard deviation of scores, on 27 tests, for 58 patients, the number and proportion of a group of patients, further divided according to sex and chronicity, showing scores beyond the range of normal values on these tests, and the critical ratio of the difference between the proportion of these patients showing abnormal test values and the proportion to be expected in a physically normal group, which is taken to be zero. Those critical ratios of 4.00 or larger have been regarded here as statistically significant.

The critical ratios were calculated, using the following method:

$$N = \text{Total number of patients}$$

$$p = \frac{\textit{Number of normal cases} \times 100}{N}$$

$$q = 100 - p$$

$$\text{S.E.} = \text{Standard error} = \sqrt{\frac{pq}{N}}$$

$$\text{CR} = \text{Critical ratio} = \frac{q}{\text{S.E.}}$$

Critical ratios greater than 3.00 are customarily accepted as indicating a difference too large to be expected to have occurred by chance. When data conform to the Gaussian curve, the probability of obtaining a critical ratio of 3.00 or more by chance is approximately 3 in 1,000. This probability may be higher or lower in distribution curves which deviate from the Gaussian form. In the present study most of the 27 tests give distribution curves for these 58 subjects which are skewed to a greater or less extent. Furthermore, the distribution curves for very high or very low proportions are in themselves somewhat skewed. It is possible that these particular deviations from Gaussian form operate to decrease the likelihood of a chance occurrence of critical ratios as large as 3.00. If they do, then critical ratios smaller than 3.00 might be

* Popper, H.: Personal communciation to the authors.

† Chaney, A. L.: Chaney Modification, Method for Lipid Phosphorus: Personal communication to the authors.

‡ References 15 and 16.

§ References 1 and 17.

regarded as statistically significant. However, the various deviations from Gaussian form may affect the values of the critical ratios in the opposite direction. Because of this possibility, it was considered best to allow a wide margin of safety and to accept as definitely significant only those differences yielding critical ratios of 4.00 or more. If there is error here, it is undoubtedly on the side of being overly cautious. Certainly in any interpretation of these data, differences showing critical ratios between 3.00 and 4.00 should be regarded as possibly, or probably, significant.

RESULTS

General Analysis

Of a total of 1,566 determinations made on 58 patients, 239 determinations (15.26%) were found to be abnormal. Of the 239 abnormal determinations, 75

TABLE 1.—*Normal Ranges for Twenty-Seven Hepatic Function Tests and Mean Test Values in Fifty-Eight Multiple Sclerosis Patients*

Test and Unit of Measurement	Normal Ranges	Test Values Among 58 Patients	
		Mean	S.D.
Phenol turbidity, mg. per 100 cc.	0-30	13.9	5.9
Total lipid turbidity, mg. per 100 cc.	400-800	683.2	139.7
Total cholesterol, mg. per 100 cc.	125-250	229.0	6.8
Free cholesterol, mg. per 100 cc.	0-60	55.22	16.6
Free/total cholesterol, %	0-60	24.45	5.5
Cholesterol esters, mg. per 100 cc.	0-190	173.12	46.6
Cholesterol esters/total cholesterol, %	>60	75.30	6.41
Lipid phosphorus, mg. per 100 cc.	8-11	10.44	2.7
Serum esterase, γM/ml.	>15	17.74	4.09
Alkaline phosphatase, Bodansky units	0-4	2.09	1.36
Inorganic phosphorus, mg. per 100 cc.	2-4	3.85	0.79
Total van den Bergh, mg. per 100 cc.	0-1.2	0.85	0.32
Urinary bilirubin	0	.....	....
Urinary urobilinogen	0-1+	0.58	1.07
Sulfobromophthalein retention, %	0-5	3.04	2.13
Total protein, gm. per 100 cc.	6.0-8.0	7.04	0.43
True albumin, gm. per 100 cc.	3.6	4.09	0.47
True globulin, gm. per 100 cc.	1.0-3.0	2.95	0.44
True albumin-globulin ratio	>1.0	1.422	0.29
Howe albumin, gm. per 100 cc.	4-5	4.89	0.39
Howe globulin, gm. per 100 cc.	.....	2.15	0.28
Howe albumin-globulin ratio	>2.0	2.31	0.37
Gamma globulin, gm. per 100 cc.	0.7-1.25	1.04	0.22
Mucoprotein, mg. tyrosine per 100 cc.	2-4	2.90	1.3
Cephalin flocculation	0-1+	0.224	0.77
Thymol turbidity, units	0-5	2.88	1.91
Zinc sulfate turbidity, units	6-12.5	10.74	3.57

(31.4%) were found among the 13 (22.4%) male patients and 164 (68.6%) among the 45 (77.6%) female patients.

The mean averages of the various functions tested among the 58 patients were within the normal ranges of normal (Table 1).

The greatest number of abnormalities were found in the total cholesterol, cholesterol esters, lipid phosphorus, and inorganic phosphorus. Statistically significant abnormalities, when their incidence in our group is compared with that which may be present in a normal population, were found, in order of greatest significance of abnormality present, in lipid phosphorus, inorganic phosphorus, cholesterol esters, total cholesterol, true globulin, Howe albumin, zinc sulfate turbidity, and serum esterase.

Among the 14 patients in the acute phase of the disorder, no statistically significant abnormalities were present, though the values of total cholesterol, cholesterol esters, and lipid phosphorus were much higher than other tests, but still below the top normal value for the normal critical ratio.

Among the 44 patients in the chronic stationary or slowly progressive phase of the disorder, statistically significant abnormalities, in the order named, were found in lipid phosphorus, inorganic phosphorus, cholesterol esters, total cholesterol, true globulin, and Howe albumin.

TABLE 2.—*Distribution of Abnormal Values for Twenty-Seven Hepatic Function Tests in Fifty-Eight Multiple Sclerosis Patients*

	Abnormal Tests Among 58 Patients			Distribution by Sex		Abnormal Tests Among 14 Patients with Acute Exacerbations			Abnormal Tests Among 44 Patients in Chronic or Slowly Progressive Phase		
Test	No.	%	C.R.	M	F	No.	%	C.R.	No.	%	C.R.
Phenol turbidity	1	1.72	0.988	1	0	1	7.14	1.037	0	0	0
Total lipid turbidity	12	20.68	3.908	4	8	2	14.29	1.529	10	22.72	3.602
Total cholesterol	21	36.20	5.724	8	13	6	42.86	3.242	15	34.09	4.775
Free cholesterol	0	0	0	0	0	0	0	0	0	0	0
Free/total cholesterol	0	0	0	0	0	0	0	0	0	0	0
Cholesterol esters	22	37.93	5.962	7	15	6	42.86	3.242	16	36.36	5.019
Cholesterol esters/total cholesterol	0	0	0	0	0	0	0	0	0	0	0
Lipid phosphorus	23*	39.65	6.162	6	17	5	35.71	2.789	18	40.99	5.540
	9†	15.51	3.274	1	8	2	14.29	1.529	7	15.90	2.890
Serum esterase	13	22.41	4.093	2	11	3	21.42	1.956	10	22.72	3.602
Alkaline phosphatase	4	6.89	2.050	2	2	2	14.29	1.529	2	4.54	1.458
Inorganic phosphorus	22	37.93	5.962	7	15	5	35.71	2.789	17	38.63	5.229
Total van den Bergh	6	10.71	2.600	2	4	3	21.42	1.956	3	7.14	1.805
Urinary bilirubin	2	3.57	1.461	0	2	1	7.14	1.037	1	2.38	1.000
Urinary urobilinogen	8	14.28	3.046	2	6	0	0	0	8	19.04	3.148
Sulfobromophthalein retention	9	15.78	3.290	2	7	4	28.57	2.367	5	11.62	2.383
Total protein	2	3.57	1.493	1	1	0	0	0	2	4.54	1.458
True albumin	2	3.57	1.493	1	1	0	0	0	2	4.54	1.458
True globulin	19	32.75	5.314	5	14	3	21.42	1.956	16	36.36	5.019
True albumin-globulin ratio	5	8.62	2.364	2	3	0	0	0	5	11.36	2.378
Howe albumin	16	27.58	5.996	2	14	2	14.29	1.529	14	31.81	4.532
Howe globulin	0	0	0	0	0	0	0	0	0	0	0
Howe albumin-globulin ratio	9	15.51	3.274	3	6	0	0	0	9	20.45	3.360
Gamma globulin	9	15.51	3.274	5	4	2	14.29	1.529	7	15.90	2.890
Mucoprotein	12*	20.68	3.908	5	7	3	21.42	1.956	9	20.45	3.360
	12†	20.68	3.908	3	9	3	21.42	1.956	9	20.45	3.360
Cephalin flocculation	4	6.89	2.050	1	3	1	7.14	1.037	3	6.81	1.794
Thymol turbidity	4	6.89	2.050	1	3	1	7.14	1.037	3	6.81	1.794
Zinc sulfate turbidity	14	24.13	4.310	6	8	3	21.42	1.956	11	25.00	3.834

* Number of instances above upper limit of normal test value.
† Number of instances below lower limit of normal test value.

Of the 27 tests done in the total group of 58 patients, none were found to be abnormal in 1 patient, a 44-year-old woman. One test was abnormal in seven patients, five women and two men. Two tests were abnormal in 10 patients, all women. Three tests were abnormal in nine patients, eight women and one man. Four tests were abnormal in four patients, two women and two men. Five tests were abnormal in 12 patients, 11 women and 1 man. Six tests were abnormal in six patients, five women and one man. Seven tests were abnormal in five patients, two women and three men. Eight tests were abnormal in one woman. Nine, 10 and 11 tests were abnormal in one patient each, every one a man (Table 2).

LIPIDS

Swank,[18] in a recent survey of wartime, prewar, and postwar (World War II) incidence of multiple sclerosis in countries where there is an over-all relatively high incidence of this disease (Norway, Sweden, Denmark, Netherlands, Belgium, England, and Switzerland), found a proportionately high fat consumption, especially of animal fat, where the incidence of multiple sclerosis was high. He concluded that a high fat diet is not the cause of multiple sclerosis, even though it may contribute to a high incidence of the disease by accelerating it in susceptible persons.

Wilmot and Swank,[19] in an attempt to determine whether the amount and type of fat intake can be correlated with the incidence of multiple sclerosis, observed multiple sclerosis patients as well as normal subjects, both while on a usual and while on a low fat diet. They found no essential differences between normal subjects and patients with multiple sclerosis with respect to either lipid levels or the response of lipid levels to a change to a low fat diet. They also found total lipid values of 639 (range 486-765) mg. per 100 cc. in multiple sclerosis patients and of 591 (range 477-722) mg. per 100 cc. in normal subjects.

Cholesterol.—Wilmot and Swank [19] made determinations of total and free cholesterol and cholesterol esters in 15 patients with multiple sclerosis and in 14 normal subjects. A total of 44 determinations were made in the 15 multiple sclerosis patients and 43 in the 14 normal subjects. The average total cholesterol value in the multiple sclerosis patients was 194 (range 140-244) mg. per 100 cc. and in normal subjects 188 (range 112-241) mg. per 100 cc. The average cholesterol esters value was 138 (range 101-167) mg. per 100 cc. in multiple sclerosis patients and 129 (range 68-169) mg. per 100 cc. in normal subjects. The average free cholesterol value was 56 (range 39-72) mg. per 100 cc. in multiple sclerosis patients and 59 (range 43-82) mg. per 100 cc. in normal subjects. These authors conclude that in their group of patients there was no essential difference in the blood cholesterol content between normal and multiple sclerosis subjects.

Chiavacci and Sperry [20] reported their observations on total cholesterol and "combined in total cholesterol" values in 52 patients with multiple sclerosis, using the Schoenheimer-Sperry method in their determinations. With the exception of a few cases, they used an aqueous, and not an alcoholic, solution of digitonin in their studies. Eleven of these patients, consisting of 8 males and 3 females, showed an elevation of total cholesterol above 250 mg. per 100 cc., and 41 patients, consisting of 18 males and 23 females, showed values below 250 mg. per 100 cc. They reported an average value of 203.5± 47.2 (S.D.) mg. per 100 cc. They concluded that the number of patients showing an elevation was not statistically significant and that hypercholesterolemia was not present in their group of 52 patients. The percentage of "combined in total cholesterol" in all of the 52 patients was above 60, a value which they concluded to be within normal limits. They also were of the opinion that age does not seem to be a factor in the cholesterol value in their series of patients.

Fog [21] reported that he found no abnormalities of blood cholesterol, free or esterified, in multiple sclerosis patients.

Jones, Jones, and Bunch [22] studied the total and esterified cholesterol in multiple sclerosis patients, of whom 25 were in relapse and 38 in remission, as well as in 30 control subjects. They reported total cholesterol values of 271.1 ± 6.7 mg. per 100 cc. in 25 patients with relapse, 266.5 ± 7.14 mg. per 100 cc. in 38 patients with remission, and 230 ± 7.41 mg. per 100 cc. in 30 control subjects. They considered

the total cholesterol to be significantly elevated and a constant finding in their group of multiple sclerosis patients, stating that in individual patients a fall in cholesterol generally paralleled clinical improvement. The cholesterol esters in the same group of multiple sclerosis patients increased, and the per cent of total cholesterol esterified ranged from 65 to 80 with no exceptions.

Altmann and Goldhammer,[23] using the Rappaport and Engelberg methods [24] for cholesterol determinations, reported that 14 out of 16 patients with multiple sclerosis, or 87%, showed cholesterol values ranging from 230 to 460 mg. per 100 cc., an observation which they termed substantial evidence of hypercholesterolemia.

Pichler and Reisner [25] studied the total, free, and esterified cholesterol values for 10 patients with acute, and for 28 patients with stationary or slowly progressive, multiple sclerosis, using the methods of Rappaport and Engelberg.[24] Their normal value for total cholesterol was 100 to 160 mg. per 100 cc., and for cholesterol esters 60 to 70% of total cholesterol. In the 10 acute cases they reported findings which were as follows: total cholesterol, mean 182 (range 150-242) mg. per 100 cc., cholesterol esters, mean 127 (range 94-167) mg. per 100 cc., and cholesterol ester-total cholesterol ratio, mean 69.7% (range 58.2-83.9%). In the 28 chronic cases the values were as follows: total cholesterol, mean 140 (range 110-167) mg. per 100 cc., cholesterol esters, mean 99 (range 74-135) mg. per 100 cc., and cholesterol ester-total cholesterol ratio, mean 70.7% (range 60-82%). These authors reported a fluctuation in the cholesterol values, with a distinct increase in serum cholesterol in acute cases and a return to normal on clinical improvement.

Frisch [26] reported a similar study in 12 patients with multiple sclerosis, using the same methods. His normal range for total cholesterol was reported as 120-180 mg. per 100 cc. His findings in the multiple sclerosis patients were as follows: total cholesterol, average 258.6 (range 192.7-315.2) mg. per 100 cc., with seven patients having values above 250 mg. per 100 cc.; cholesterol esters, average 179 (range 126.7-212.4) mg. per 100 cc., with three patients having values above 190 mg. per 100 cc., and cholesterol ester-total cholesterol ratio, average 69.2% (range 63.5-75.2%). The author considered the total cholesterol values for his patients to be extremely high and the free and esterified cholesterol ratios normal.

In our studies cholesterol values, total and esterified, were elevated jointly in 19 patients. The total cholesterol was elevated in two patients, and cholesterol esters alone, in three patients. The ratio of cholesterol esters to total cholesterol and the ratio of free to total cholesterol were normal in all instances. There was no significant difference in the incidence between male and female patients; neither was there any correlation with age.

Lipid Phosphorus Studies.—Chiavacci and Sperry [20] reported lipid phosphorus studies in 52 patients with multiple sclerosis. The average value was 8.4 ± 1.72 (S.D.) mg. per 100 ml., and these authors concluded that the concentration of lipid phosphorus in patients with multiple sclerosis bore the same mathematical relationship to the cholesterol concentration as that which has been reported for normal persons.

Fog [21] reported normal lipid phosphorus values in patients with multiple sclerosis.

Laignel-Lavastine and Koressios [27] reported that of 16 patients with multiple sclerosis lipid phosphorus studies showed increased values in 5 patients, 4 of whom were in the active and 1 in the inactive phase clinically; decreased values in 4 patients, of whom 1 was in the active and 3 in the inactive phase; variations from

TABLE 3.—*Lipid Studies in Fifty-Eight Multiple Sclerosis Patients*

Age and Sex of Patient		Phenol Turbidity, Mg. per 100 Cc.	Total Lipid Turbidity, Mg. per 100 Cc.	Total Cholesterol, Mg. per 100 Cc.	Free Cholesterol, Mg. per 100 Cc.	Free/Total Cholesterol, %	Cholesterol Esters, Mg. per 100 Cc.	Cholesterol Esters/Total Cholesterol, %	Lipid Phosphorus, Mg. per 100 Cc.
(Normal)		0-30	400-800	125-250	0-60	0-60	0-190	>60	8-11
18	Fa*	10.9	640	113	32	28.31	81	71.6	9.2
21	F	14.8	660	202	37	18.31	165	81.6	11.9†
22	F	6.6	514	167	32	19.16	135	80.8	10.9
23	F	17.7	470	158	75	47.46	83	52.5†	7.1†
23	F	11.6	710	156	25	16.02	131	83.9	10.2
24	Ma*	9.4	560	194	50	25.77	144	74.2	9.0
24	F	9.1	580	165	40	24.24	125	75.7	8.7
25	F	20.9	770	270†	48	17.77	222†	82.2	11.2†
25	Fa	12.6	400	190	41	21.57	149	78.4	9.6
27	Fa	15.1	660	295†	55	18.64	240	81.3	11.0
27	Fa	7.2	580	180	55	30.55	125	69.4	13.7†
28	F	28.8	900†	310†	100	32.25	210†	67.7	12.4†
29	Fa	13.3	640	250	43	17.20	207†	82.8	10.1
30	Fa	9.4	540	211	48	22.74	163	77.2	9.8
30	Fa	5.3	453	162	34	20.98	128	79.0	7.0†
30	F	12.2	820†	137	43	31.38	94	68.6	11.2†
31	M	19.8	640	285†	60	21.05	225†	78.9	9.0
31	F	13.3	680	250	60	24.00	190	76.0	6.3†
31	F	11.6	640	259†	49	18.91	210†	81.0	5.1†
31	F	11.6	560	296†	41	13.85	255†	86.1	9.9
31	Fa	21.6	845†	285†	73	25.61	202†	70.8	11.2†
32	F	12.6	700	224	54	24.10	170	75.8	6.0†
33	Ma	11.6	690	255†	62	24.31	193†	75.6	10.5
33	Ma	16.1	760	277†	80	28.88	197†	71.5	11.3†
33	F	12.9	453	168	45	26.78	123	73.2	7.9†
33	F	8.4	505	210	63	30.00	147	70.0	10.8
33	F	16.6	720	234	60	25.64	174	74.3	9.6
33	F	8.1	522	168	40	23.80	128	76.1	9.3
34	M	10.3	660	209	39	18.66	170	81.3	10.8
34	Fa	13.6	720	137	39	28.46	98	71.5	14.1†
35	M	17.1	845†	252†	59	23.41	193†	76.5	9.9
35	F	10.0	480	190	48	25.26	142	74.7	5.8†
35	F	5.3	523	161	31	19.25	130	80.7	8.9
37	F	13.6	680	181	40	22.09	141	77.9	9.6
37	F	5.8	540	168	40	23.80	128	76.1	8.2
38	M	20.2	720	277†	62	22.38	215†	77.6	12.5†
38	F	18.1	770	299†	48	16.05	251†	83.9	11.4†
38	F	11.2	580	168	49	29.16	119	70.8	17.0†
39	F	12.2	680	230	50	25.65	171	74.3	9.3
39	F	14.0	660	249	49	19.67	200†	80.3	8.7
41	Ma	38.4†	1,170†	360†	95	26.38	265†	73.6	19.5†
41	F	8.2	660	248	61	24.59	177	71.3	10.0
41	F	20.9	760	230	50	20.83	180	78.2	12.2†
44	F	10.0	700	199	42	21.10	157	78.8	10.8
45	F	14.0	700	269†	43	15.98	226†	84.0	12.6†
45	Fa	18.1	550	300†	60	20.00	240†	80.0	4.7†
50	F	7.2	820†	249	49	19.67	200†	80.3	8.6
51	M	8.8	720	261†	76	29.11	185	70.8	10.8
51	F	19.2	872†	200	99	49.50	101	50.5	14.1†
51	F	10.3	720	240	65	27.08	175	73.0	11.9*
51	F	13.8	810†	270†	80	29.62	190	70.5	14.3†
52	M	8.4	900†	278†	80	28.77	198†	71.2	7.3†
54	M	8.9	700	178	58	32.58	120	67.4	12.6†
54	F	21.6	820†	318†	67	21.06	251†	78.9	12.6†
55	M	18.9	720	234	61	26.06	173	73.9	11.1†
56	M	14.2	880†	238	69	28.99	169	71.0	11.7†
57	F	21.6	760	300†	70	23.33	230†	76.6	12.6†
64	F	23.0	886†	300†	70	23.33	230†	76.6	12.2†

* In this column, a indicates acute case.
† Abnormal value.

normal to increased values in 4 patients, of whom 2 were in the active and 1 in the inactive phase, and normal values in 3 patients, who were all in the inactive phase of the disorder. Patients showing increased lipid phosphorus levels were in the 38- to 59-year age group; those showing decreased values were in the 25- to 38-year age group; those showing variations from normal to increased value were in the 40- to 59-year age group, and those with normal values were in the 48- to 58-year age group. These authors give the range of normal for phospholipids as 1.1-1.4 mg. per cc. of serum.

Wilmot and Swank [19] found no significant differences between normal controls and multiple sclerosis patients, who were on a usual diet, in their fasting plasma lipid levels. Forty-four determinations were made in 15 patients with multiple sclerosis, and 43 determinations, in 14 normal subjects. The average phospholipid level in patients with multiple sclerosis was reported as 218 (range 176-272) mg. per 100 cc., and in normal controls as 214 (range 177-268) mg. per 100 cc. On a low fat diet both the normal and the multiple sclerosis subjects showed a reduction in the phospholipid and cholesterol levels with a return of the phospholipids, but not of the cholesterol, to a predietary level in both groups of patients.

In our studies phenol turbidity was elevated in one patient only, a 41-year-old man in an acute phase of the disease. In this patient phenol turbidity, total lipid turbidity, total cholesterol, cholesterol esters, and lipid phosphorus were also elevated. Of the last four tests named, all four were elevated in four patients, three in 9 patients, two in 9 patients, and only one in 12 patients. The greatest incidence was among chronic patients (Table 3).

Enzymes

Serum Esterase.—Crandall and Cherry [28] were able to show no significant changes in the serum esterase (active on ethyl butyrate) in the blood of 27 multiple sclerosis patients and that of 131 controls, the latter including 10 patients with liver disease and 17 patients with diseases of the central nervous system other than multiple sclerosis.

Brickner [29] reported data derived from a study of 62 patients with multiple sclerosis, 47 of whom were in the active, and 15 in the inactive, phase of the disease. He concluded that during activity of the disease serum esterases are normal in their degree of action, and that during inactivity of the disease the activity of the esterases rises to a level considerably above normal.

Brickner, Watters, Wexler, and Soltz [30] reported essentially the same conclusions in their report of 89 patients with multiple sclerosis.

Richards and Wolff [31] described a manometric method which they deemed more accurate and convenient than titration for determination of esterases, lipase, and cholinesterase activity of serum. They reported observations of 143 determinations in 30 multiple sclerosis patients, 78 determinations in 42 patients with disease of the central nervous system other than multiple sclerosis, and 24 determinations in 13 normal persons. They found no difference in the behavior of serum from patients with multiple sclerosis and serum from any other persons. Moreover, no change in the activity of these enzymes has been demonstrated during remission or exacerbation of the signs and symptoms of multiple sclerosis.

Serum Phosphatase.—Jones, Jones, and Bunch [22] reported in their observations on 50 patients with multiple sclerosis and 30 control subjects that serum alkaline phosphatase was normal in every case.

TABLE 4.—*Enzyme, Bilirubin, Obstructive Mechanisms, and Sulfobromophthalein Retention Studies in Fifty-Eight Multiple Sclerosis Patients*

Age and Sex of Patient		Serum Esterase, γM/Ml.	Alkaline Phosphatase, Bodansky Units	Inorganic Phosphorus, Mg. per 100 Cc.	Total van den Bergh, Mg. per 100 Cc.	Urinary Bilirubin	Urinary Urobilinogen	Sulfobromophthalein Retention, %
(Normal)		>15	0-4	2-4	0-1.2	0	0-1+	0-5
18	Fa*	19.6	2.6	4.2†	0.2	0	1+	3.0
21	F	14.5†	1.6	2.4	0.9	0	0	1.0
22	F	12.0†	2.6	2.8	1.2	0	2+†	3.0
23	F	14.5†	2.2	5.4†	0.8	0	1+	1.0
23	F	18.7	1.1	5.5†	0.7	0	4+†	1.0
24	Ma*	15.5	3.8	4.2†	0.7	0	1+	0.3
24	F	21.2	2.3	3.4	0.6	0	Tr	2.5
25	F	18.7	1.3	3.5	1.2	0	0	3.0
25	Fa	20.4	4.0	3.6	1.4†	0	0	1.2
27	Fa	26.1	1.2	3.3	1.3†	0	0	3.0
27	Fa	17.5	1.3	4.0	0.6	Tr†	Tr	5.6†
28	F	21.1	3.0	2.4	1.6†	0	4+†	4.0
29	Fa	15.5	2.0	3.4	0.8	0	0	1.0
30	Fa	17.3	3.6	3.6	1.0	0	Tr	5.3†
30	Fa	18.0	2.1	4.5†	1.0	0	0	9.0†
30	F	17.5	1.2	5.6†	0.8	0	4+†	7.0†
31	M	22.2	4.0	3.6	0.9	0	2+†	2.0
31	F	18.0	3.6	4.2†	0.7	0	1+	3.5
31	F	19.1	3.3	4.5†	0.6	0	0	5.0
31	F	14.5†	1.9	2.7	1.1	0	0	1.0
31	Fa	18.4	2.2	4.0	0.9	0	0	5.0
32	F	20.3	1.4	4.0	...	0	2+†	...
33	Ma	13.0†	2.0	3.2	1.2	0	0	1.5
33	Ma	14.5†	4.5†	4.3†	0.6	0	0	5.5†
33	F	11.9†	3.2	3.0	0.3	0	0	1.0
33	F	15.5	1.7	3.6	0.6	0	0	1.0
33	F	21.2	3.6	3.4	0.6	..	..	2.0
33	F	15.5	2.6	4.5†	0.6	0	0	1.0
34	M	20.9	3.4	3.6	0.8	0	0	1.0
34	Fa	27.2	3.0	4.4†	1.2	0	1+	1.5
35	M	16.0	4.0	3.8	0.9	0	2+†	1.0
35	F	21.2	1.6	4.2†	0.8	0	0	1.5
35	F	10.9†	2.8	5.0†	1.0	0	1+	3.0
37	F	13.7†	1.8	2.2	0.5	0	2+†	0.8
37	F	15.5	2.0	3.0	0.7	0	1+	7.0†
38	M	15.2	1.2	4.1†	1.5†	0	0	3.0
38	F	12.7†	3.4	4.8†	0.6	0	0	4.0
38	F	9.9†	2.8	3.8	1.1	0	0	1.0
39	F	18.0	3.1	3.3	0.8	0	Tr	4.1
39	F	10.9†	2.8	3.6	0.7	0	0	5.0
41	Ma	18.9	2.7	3.7	1.4†	0	0	3.0
41	F	15.5	0.7	4.1†	0.9	0	1+	1.5
41	F	15.0	2.3	3.8	0.8	0	0	7.5†
44	F	18.7	1.2	3.5	0.9	0	1+	4.5
45	F	29.1	3.6	2.6	2.0†	0	1+	1.5
45	Fa	20.9	4.2†	3.6	0.6	0	0	2.0
50	F	21.6	2.2	4.2†	0.9	0	0	1.5
51	M	15.7	1.6	4.3†	0.7	0	0	1.2
51	F	18.4	1.1	3.9	0.5	Tr†	Tr	4.0
51	F	20.4	4.0	3.3	0.7	0	0	1.0
51	F	22.7	2.4	5.7†	0.7	0	0	1.0
52	M	25.5	1.4	3.6	...	0	0	5.6
54	M	15.0	7.9†	4.6†	0.6	..	..	4.0
54	F	13.2†	7.4†	3.4	0.75	0	Tr	5.0
55	M	15.0	2.4	4.5†	0.9	0	0	8.0†
56	M	15.5	1.9	4.6†	0.7	0	Tr	5.0
57	F	21.6	4.0	3.7	0.9	0	0	2.0
64	F	22.1	3.6	3.8	0.7	0	Tr	6.3†

* In this column, a indicates acute case.
† Abnormal value.

Fog [21] also reported no abnormalities in the serum phosphatase in patients with multiple sclerosis.

Inorganic Phosphorus.—Weil and Cleveland,[32] using the method of Fiske and SubBarow,[5] examined 46 patients with multiple sclerosis, making 79 determinations on inorganic phosphorus. The average reading was 3.4 mg. per 100 cc. In 40% of the cases the serum inorganic phosphorus was below 3.3 mg. per 100 cc., and in 65% it was 3.5 mg. per 100 cc. or less. The average value of serum inorganic phosphorus in normal controls was 4 mg. per 100 cc., in 21 cases of various diseases 4.2 mg. per 100 cc., and in central nervous system syphilis 4.4 mg. per 100 cc.

Jones, Jones, and Bunch [22] found a consistently low serum inorganic phosphorus in their series of 50 multiple sclerosis patients. Patients in relapse showed values of 3.82 mg. per 100 ml.; those in remission, 3.57 mg. per 100 ml., and 30 control subjects, 3.92 mg. per 100 ml.

In our studies the serum esterase was reduced below 15 μM per milliliter in 13 patients. Four patients had an elevated alkaline phosphatase above 4 Bodansky units, the highest being 7.9 Bodansky units. Inorganic phosphorus was elevated above 4 mg. per 100 cc. in 22 patients, of whom 5 had elevations above 5 mg. per 100 cc., the highest being 5.7 mg. per 100 cc.

Abnormalities of all three of these tests were found in 1 patient, of two of these tests in 3 patients, and of one only in 24 patients.

There was no significant correlation between age or sex in the incidence of the test abnormalities (Table 4).

Proteins

Total Protein.—Jones, Jones, and Bunch [22] reported that serum proteins in 50 patients with multiple sclerosis were lower than in normal persons, though not significantly so.

Putnam [33] reported a lower level of fibrinogen in 13 cases of multiple sclerosis than in 3 control subjects. This was accompanied by an increase in the euglobulin portion of the curve, which was much higher in multiple sclerosis than in the controls. The excess of euglobulin was seen in the range in which the curve for prothrombin occurred.

Swank, Franklin, and Quastel [34] described what they considered as significant changes in plasma protein with abnormal pattern with paper chromatography technique in the active phase of multiple sclerosis which reverted to normal during remissions.

Bagni and Andreani [35] conducted refractometric determinations of the serum total protein combined with sedimentation rate (Westergren method) for the determination of the so-called index of Katz. Elevated serum total protein was found in 5 of the multiple sclerosis patients studied. The sedimentation rate (evaluated after the index of Katz) and serum proteins were slightly elevated in nine cases.

Serum Albumin and Globulin.—Fog [21] reported normal findings of serum albumin and globulin in his group of multiple sclerosis patients.

Gamma Globulin.—Kabat, Freedman, and Murray [36] examined the cerebrospinal fluid of 100 multiple sclerosis patients for albumin and gamma globulin levels. Eighty-five per cent of the multiple sclerosis patients showed significant elevation in the cerebrospinal fluid gamma globulin. Significantly, these authors stated that increases in the cerebrospinal fluid gamma globulin are also seen if the serum gamma

globulin is increased, since part of the cerebrospinal fluid protein is derived from the plasma protein.

Cephalin Flocculation.—Jones, Jones, and Bunch [22] studied the cephalin flocculation by the Hanger [14] method in 50 cases of multiple sclerosis. The cephalin flocculation was positive in 50% of their patients, which, the authors state, is not different from the findings in a miscellaneous group of chronically ill patients with diseases other than multiple sclerosis.

Thymol Turbidity.—Fog [21] reported normal thymol turbidity in his group of multiple sclerosis patients.

Bagni and Andreani [35] did thymol turbidity tests on 20 multiple sclerosis patients and found strongly positive values in 1 patient and weakly positive values in 5 patients.

In our studies the total protein was above 8 gm. per 100 cc. in two patients. True albumin was insignificantly lowered below 3 gm. per 100 cc. in two patients. True globulin was above 3 gm. per 100 cc. in 19 patients, above 4 gm. per 100 cc. in 1 patient, and not less than 2.3 gm. per 100 cc. in any patient. The true albumin-globulin ratio was slightly less than 1 in five patients. Howe albumin was not less than 4.15 gm. per 100 cc. in any patient and was above 5 gm. per 100 cc. in 16 patients. There was no clear relation between the value for the true and the value for the Howe albumin levels. The Howe albumin-globulin ratio was above 1.55 in all patients and less than 2 in nine patients. Gamma globulin was elevated above 1.25 gm. per 100 cc. in nine patients, the highest value being 1.56 gm. per 100 cc. Mucoprotein was less than 2 mg. of tyrosine per 100 cc. in 12 patients and above 4 mg. of tyrosine per 100 cc. in 12 patients. Cephalin flocculation was above 1 + in four patients. Four patients had an elevation of thymol turbidity above 5 units. Zinc sulfate turbidity was elevated above 12.5 units in 14 patients, 1 of whom had a value of 21.9 units.

Of the 12 different tests done in the study of the protein function, a total of 8 were abnormal in 1 patient, 7 in 1 patient, 6 in 2 patients, 5 in 1 patient, 4 in 3 patients, 3 in 6 patients, 2 in 7 patients, and only 1 in 19 patients.

There was no significant difference in the number of abnormalities found with respect to age (Table 5).

Bilirubin Excretion

Serum and Urinary Bilirubin.—Jones, Jones, and Bunch [22] reported normal serum bilirubin findings in a group of 50 patients with multiple sclerosis.

Fog [21] also reported normal serum bilirubin findings in his group of multiple sclerosis patients.

Dekaban, Brodrick, and Waugh [37] examined serum bilirubin in 80 patients with multiple sclerosis, of whom 6 (7%) had the acute, 31 (39%) the progressive, and 43 (54%) the classic form of multiple sclerosis. In only two patients, both of whom were among the six acute cases, was serum bilirubin elevated (1.92 and 1.38 mg. per 100 cc.).

Bagni and Andreani [35] reported on serum bilirubin in 20 patients with multiple sclerosis and found four abnormalities in this group of patients.

In our studies the serum bilirubin was insignificantly elevated above 1.2 mg. per 100 cc. in six patients, the highest elevation being 2 mg. per 100 cc. in one patient.

Urinary bilirubin showed only a "trace" of elevation in two patients.

TABLE 5.—*Plasma Protein Studies in Fifty-Eight Multiple Sclerosis Patients*

Age and Sex of Patient		Total Protein, Gm. per 100 Cc.	True Albumin, Gm. per 100 Cc.	True Globulin, Gm. per 100 Cc.	True A/G Ratio	Howe Albumin, Gm. per 100 Cc.	Howe Globulin, Gm. per 100 Cc.	Howe A/G Ratio	Gamma Globulin, Gm. per 100 Cc.	Mucoprotein, Mg. Tyrosine per 100 Cc.	Cephalin Flocculation	Thymol Turbidity, Units	$ZnSO_4$ Turbidity, Units
(Normal)		6-8	3	1-3	>1	4-5		>2.0	0.7-1.25	2-4	0-1+	0-5	6-12.5
18	Fa*	7.32	4.50	2.82	1.58	5.00	2.32	2.15	1.14	1.7†	0	1.4	7.6
21	F	7.25	4.78	2.67	1.67	5.26†	1.99	2.64	1.09	4.5†	0	3.8	9.2
22	F	6.45	3.92	2.53	1.55	4.49	1.96	2.29	0.82	2.7	0	2.8	9.2
23	F	7.90	4.79	3.11†	1.54	5.70†	2.20	2.60	1.16	4.5†	0	3.3	12.2
23	F	6.53	4.21	2.31	1.80	4.39	2.14	2.05	0.95	4.2†	0	1.6	6.6
24	Ma*	6.64	4.02	2.62	1.53	4.85	1.92	2.65	0.81	3.4	0	2.0	5.8
24	F	6.60	3.39	3.21†	1.06	4.40	2.20	2.00	0.31	2.2	0	2.5	8.6
25	F	6.42	3.87	2.55	1.51	4.52	1.90	2.38	0.82	2.0	0	2.8	7.2
25	Fa	7.40	4.61	2.79	1.71	5.05	2.35	2.15	1.31†	4.4†	0	8.4†	13.6†
27	Fa	7.27	4.19	3.08	1.36	4.95	2.32	2.13	1.33†	2.7	0	3.7	18.6†
27	Fa	7.00	4.03	2.97	1.36	5.02	1.98	2.54	1.12	7.2†	3+†	2.7	8.4
28	F	7.67	5.11	2.56	2.00	5.70†	1.97	2.89	0.98	2.3	0	3.0	9.4
29	Fa	6.57	3.40	3.17†	1.07	4.63	1.94	2.38	0.87	2.5	0	2.0	7.2
30	Fa	6.57	3.77	2.80	1.35	4.58	1.99	2.30	0.84	4.3†	0	1.4	10.0
30	Fa	7.32	4.09	3.23†	1.27	5.32†	2.00	2.66	1.09	3.1	0	3.5	13.3†
30	F	6.90	4.05	2.85	1.42	4.97	1.93	2.57	0.98	3.25	0	2.3	8.4
31	M	7.04	4.03	3.01	1.31	4.83	2.21	2.17	0.84	1.50†	0	2.8	13.6†
31	F	7.82	4.29	3.53†	1.22	5.60†	2.22	2.56	0.98	2.5	0	4.8	10.6
31	F	7.45	4.20	3.25†	1.29	5.01	2.44	2.06	1.06	3.75	0	3.0	10.6
31	F	7.45	4.29	3.16†	1.40	5.27†	2.24	2.32	1.23	4.2†	0	2.0	10.3
31	Fa	7.18	4.83	2.35	2.06	5.35†	1.83	2.92	0.90	3.1	0	1.8	10.3
32	F	6.93	4.11	2.82	1.42	4.82	2.08	2.32	0.82	2.5	0	2.5	8.9
33	Ma	7.27	4.47	2.80	1.63	5.05	2.22	2.27	1.12	1.63†	0	2.2	11.8
33	Ma	6.50	4.01	2.49	1.61	5.00	1.50	3.33	0.76	1.30†	0	0.5	6.4
33	F	6.82	4.16	2.66	1.57	4.59	2.23	2.06	0.85	2.3	0	2.0	7.5
33	F	7.45	4.68	2.77	1.69	5.32†	2.13	2.51	1.11	3.4	0	1.6	8.9
33	F	8.13†	4.16	3.97†	1.05	5.50†	2.63	2.09	1.25	1.8†	2+†	6.1†	21.9†
33	F	7.15	4.85	2.30	2.11	5.64†	1.51	3.73	0.74	1.25†	0	1.2	6.2

34	M	7.00	4.30	2.70	1.58	4.93	2.07	2.38	1.07	5.6†	0	4.2	10.0
34	Fa	6.75	4.22	2.53	1.67	4.86	1.89	2.57	1.11	2.5	0	1.7	8.5
35	M	6.90	3.70	3.20†	1.16	4.65	2.25	2.07	0.95	2.0	0	3.5	11.2
35	F	7.00	3.73	3.27†	1.14	5.00	2.00	2.50	0.78	3.4	0	1.3	6.0
35	F	7.02	3.33	3.69†	0.91†	4.47	2.55	1.80†	1.18	3.5	0	1.4	12.2
37	F	6.50	3.96	2.54	1.56	4.50	2.00	2.25	0.73	3.0	0	4.2	12.2
37	F	6.50	3.75	2.75	1.38	4.22	2.28	1.85†	0.62	3.3	0	3.3	5.8
38	M	6.65	3.89	2.76	1.41	4.91	1.74	2.82	1.01	3.10	0	1.0	18.4†
38	F	6.75	4.08	2.67	1.53	4.77	1.98	2.51	1.13	2.0	4+†	8.0†	11.7
38	F	6.95	4.14	2.81	1.47	4.99	1.96	2.54	1.17	3.0	0	3.3	8.2
39	F	6.81	2.97†	3.74†	0.82†	4.15	2.66	1.55†	1.56†	2.8	1+	2.7	15.3†
39	F	7.15	3.77	3.38†	1.12	4.63	2.52	1.80†	1.14	2.1	0	3.0	13.3†
41	Ma	7.27	4.18	3.09	1.32	5.02	2.25	2.01	0.98	3.4	0	3.2	8.0
41	F	7.42	4.77	2.65	1.80	5.13†	2.29	2.24	1.07	2.00	0	1.9	13.5†
41	F	7.42	4.37	3.05	1.43	5.26†	2.16	2.43	1.01	1.45†	0	1.3	9.6
44	F	6.75	4.14	2.61	1.59	4.93	1.82	2.70	0.88	1.25†	0	0.8	8.8
45	F	7.35	4.53	2.82	1.60	5.17†	2.18	2.38	1.16	3.1	0	2.8	11.3
45	Fa	7.05	4.04	3.01	1.34	4.70	2.35	2.00	0.92	2.25	0	2.8	9.4
50	F	7.10	3.48	3.62	0.96†	4.61	2.49	1.85†	1.36†	1.9†	0	3.8	11.9
51	M	6.48	4.20	2.28	1.84	4.74	1.74	2.72	1.51	4.5	0	3.2	11.9
51	F	6.53	4.14	2.39	1.73	4.71	1.82	2.59	1.08	3.2	0	4.2	9.4
51	F	7.15	3.99	3.16†	1.27	4.84	2.31	2.10	0.67	1.55†	0	0.7	10.0
51	F	7.35	4.56	2.79	1.63	5.08†	2.32	2.21	1.11	1.60†	0	2.3	10.0
52	M	8.32†	4.63	3.69†	1.25	5.52†	2.80	1.98†	1.39	1.75†	3+†	10.0†	15.3†
54	M	6.48	2.75†	3.73†	0.74†	3.96	2.52	1.57†	1.32†	7.0†	0	2.8	13.4†
54	F	6.97	4.04	2.93	1.34	4.72	2.25	2.10	0.92	2.1	0	3.2	8.4
55	M	7.30	4.27	2.93	1.49	5.21†	2.09	2.54	1.53†	5.0†	0	2.5	14.4†
56	M	7.69	3.31	4.38†	0.80†	4.79	2.90	1.77†	1.08	5.4†	0	2.2	19.2†
57	F	6.47	3.84	2.63	1.46	4.33	2.14	2.03	0.62	3.5	0	1.6	5.8
64	F	6.72	3.37	3.35†	1.0	4.29	2.43	1.76†	1.56†	2.6	0	2.8	17.8†

* In this column a indicates acute case.
† Abnormal value.

Obstructive Biliary Mechanisms

Urobilinogen.—Haug [38] reported on urobilinogen determinations in 14 patients with multiple sclerosis, using the aldehyde test. Five patients showed a weakly positive reaction for urobilinogen.

In our studies urinary urobilinogen was elevated above "1 +" in eight patients, with readings of "4 +" in three patients.

Detoxifying and Dye Excretion Ability

Sulfobromophthalein.—Fog [21] reported normal findings of sulfobromophthalein excretion studies in his group of multiple sclerosis patients.

In our studies sulfobromophthalein retention was above 5% in nine patients, the highest reading being 9% in one patient, 8% in one patient, 7% in three patients, 6% in one patient, and between 5 and 6% in the others.

There was no significant correlation in age or sex of the patients, or in the acute and chronic phases of the disease in the above tests.

COMMENT

Popper and associates [39] state that hardly any of the liver function tests in common use (with the possible exception of prothrombin response to vitamin K administration) are true function tests, in the sense that they measure a basic function which is peculiar to the liver. In addition, the great regenerative ability, as well as the functional reserve of the liver, may prevent clinical and laboratory recognition of even severe morphological changes of liver cell damage. Nevertheless, a statistical analysis reveals that the results of some of the hepatic tests mirror the degree of liver cell damage, even though in individual cases this correlation does not hold true. Popper [39] further states that, although such a correlation indicates only an association, and not necessarily that the liver cell damage causes the alteration of the hepatic tests, from a practical diagnostic viewpoint, statistical analyses show which of the hepatic tests correlate best with liver cell damage. Franklin, Popper, Steigmann, and Kozoll [40] state that a significant statistical association has been observed with the albumin-globulin ratio, cephalin flocculation, thymol turbidity, and sulfobromophthalein retention. Less degrees of correlation are shown by highly elevated serum albumin and slightly elevated alkaline phosphatase. No correlation was observed with serum total protein, total cholesterol, decrease in cholesterol ester ratio, urinary urobilinogen, alkaline phosphatase in general and markedly elevated alkaline phosphatase specifically, stool urobilinogen, elevated nonprotein nitrogen, and sedimentation rate. These authors also state that with marked liver cell damage albumin-globulin ratio may be reversed and below normal with normal total protein values. This, they state, can be partly explained in the absence of an associated nephrosis by reduced synthesis of albumin by the damaged liver or increased formation of globulin by the reticuloendothelial system.

In our patients there was a depression of true albumin-globulin ratio in five patients. It was associated with abnormalities of Howe albumin-globulin ratio, true globulin, gamma globulin, and inorganic phosphorus four times; zinc sulfate turbidity three times; true albumin, mucoprotein, lipid phosphorus, and total lipid turbidity twice, and abnormalities of Howe albumin, alkaline phosphatase, and serum esterase once. A depression of Howe albumin-globulin ratio was observed in nine patients. It was associated with abnormalities of zinc sulfate turbidity six

times; gamma globulin and true globulin five times; true albumin-globulin ratio and cholesterol esters four times; true albumin, sulfobromophthalein retention, inorganic phosphorus, lipid phosphorus, and total lipid turbidity three times; mucoproteins, alkaline phosphatase, serum esterase, and total cholesterol twice, and thymol turbidity, cephalin flocculation, Howe albumin, and total protein once.

Cephalin-cholesterol flocculation is considered to correlate well with liver cell damage, since in the absence of parenchymal damage the cephalin flocculation is almost invariably negative.[40] Values greater than "1 +" are pathologic and are indicative of increased gamma globulin and reduced albumin. The cephalin flocculation test is positive in primary hepatitis, either of toxic or infectious origin, or in cirrhosis.

The cephalin flocculation test was found to be elevated in four of our patients and associated with abnormalities of thymol turbidity three times; of zinc sulfate turbidity, Howe albumin elevation but not depression, true globulin, total protein, lipid phosphorus, and cholesterol esters twice, and of sulfobromophthalein retention, gamma globulin, Howe albumin-globulin ratio, mucoprotein, urinary urobilinogen, inorganic phosphorus, serum esterase, total cholesterol, free cholesterol, and total lipid turbidity once.

Thymol turbidity is considered to show the most statistically significant correlation with liver cell damage.[40] It is closely correlated with hepatic regeneration and remains positive in infectious hepatitis longer than other tests. The elevations are indicative of increased lipids, gamma or beta globulins, or lipid protein complexes migrating with them, possibly associated with reduction of the albumin fraction.[41]

Four of our patients showed elevation of thymol turbidity. Of 9 of our patients showing elevations of gamma globulin, only 2 had elevations of thymol turbidity; of the 12 patients showing elevated total lipid turbidity, only 1 had elevated thymol turbidity, and of the 23 patients showing elevated lipid phosphorus, only 1 had elevated thymol turbidity. Elevation of thymol turbidity was associated thus with abnormalities of cephalin flocculation and zinc sulfate turbidity three times; gamma globulin, Howe albumin elevation but not depression, true globulin, total protein, lipid phosphorus, and cholesterol esters two times, and with sulfobromophthalein retention, Howe albumin-globulin ratio, serum bilirubin, urinary urobilinogen, inorganic phosphorus, serum esterase, total cholesterol, free cholesterol, and total lipid turbidity once.

A retention of sulfobromophthalein of more than 6%, 45 minutes after injection of 5 mg. of dye per kilogram of body weight, is considered pathologic due to decreased clearance of the dye from the blood. This test as performed is considered valuable only in the absence of jaundice.[41]

None of our patients were jaundiced. An elevation above 5% was present in nine patients and above 6% in five patients. Elevations of sulfobromophthalein retention were associated with abnormalities of lipid phosphorus seven times; inorganic phosphorus four times; Howe albumin-globulin ratio, elevated but not depressed Howe albumin, zinc sulfate turbidity, and mucoproteins three times; true globulin, urinary urobilinogen, cholesterol esters, and total lipid turbidity two times, and with cephalin flocculation, gamma globulin, alkaline phosphatase, serum esterase, and free cholesterol once.

High elevations of total and one-minute (direct) serum bilirubin are closely correlated with liver cell damage.[39] In the hepatogenous form, liver cell damage may cause serum bilirubin elevation; however, the ratio between total and direct bilirubin itself is not related to liver cell damage.[39]

Six of our patients showed very low elevations of serum bilirubin. It was associated with abnormalities of cholesterol esters five times; total cholesterol and lipid phosphorus four times; zinc sulfate turbidity three times; gamma globulin, Howe albumin, and total lipid turbidity twice, and with mucoprotein, thymol turbidity, urinary urobilinogen, free cholesterol, phenol turbidity, inorganic phosphorus, and true globulin once.

Minimal elevations of alkaline phosphatase, between 4 and 10 units, show some degree of correlation with liver cell damage.[40] Elevations above 10 units do not show correlation. Marked elevation is considered to be due primarily to retention of the enzyme resulting from interference with biliary excretion, as it is found chiefly in obstructive jaundice; this may account for the absence of relationship to liver cell damage.[40] In the group with values of 4 to 10 units, medical jaundice predominates. This level might be explained by a smaller degree of bile flow interference, or, as has been claimed, by an increased formation by the damaged liver cells.[40] It is believed that alkaline phosphatase is formed in the liver.[39]

Four of our patients showed slight elevations of alkaline phosphatase, the values being 4.5, 4.2, 7.9, and 7.4 Bodansky units. None of them were jaundiced. These elevations were correlated with abnormalities of lipid phosphorus, cholesterol esters, and total cholesterol three times; inorganic phosphorus and serum esterase twice; sulfobromophthalein retention, total lipid turbidity, mucoproteins, gamma globulin, true and Howe albumin-globulin ratios, true globulin, and albumin once.

The zinc sulfate turbidity becomes depressed by addition of bile and lecithin in concentrations found in serum, and because of this depression the zinc sulfate test, particularly in early stages, if depressed, points to a surgical type of obstructive jaundice, if cholangitis is excluded.[42]

None of our patients were jaundiced and none of them showed a depression of zinc sulfate turbidity. Fourteen patients showed an elevation of zinc sulfate turbidity.

Gamma globulin elevation is related to the activity of hepatic mesenchyma.[42] Basophilic material is present in the cytoplasm of hepatic epithelial and mesenchymal cells and is said to be due to the presence of pentose nucleic acids, which, in turn, have been related to protein synthesis (Casperson, 1950; Brachet, 1950). In the normal liver the epithelial cells are rich in basophilic material, whereas mesenchymal cells are almost free of it. In viral hepatitis, and especially in active cirrhosis, in which the serum albumin concentration is usually low, the epithelial cells are depleted of cytoplasmic basophilic material, but the Kupffer, histocytic, and other mesenchymal cells in the portal spaces are very rich in basophilia. The increased amount of pentose nucleic acids in the mesenchymal cells may be taken as a sign of increased protein formation, most probably of gamma globulins, which are known to be produced by mesenchymal cells. Therefore, this mesenchymal reaction (possibly a response of liver cell damage) is reflected in elevated serum gamma globulin levels. In obstructive jaundice the Kupffer cells are also proliferated but are free from cytoplasmic basophilia and pentose nucleic acids. Here the serum gamma globulin is only slightly, if at all, elevated.[42]

Nine of our patients showed elevation of gamma globulin, none of whom were associated with the two patients who had slightly depressed true albumin values. Gamma globulin elevation alone was present in two patients. Gamma globulin values below 0.7 gm. per 100 cc. were present in two patients, both showing a value of 0.62 gm. per 100 cc. Seven of the patients showing gamma globulin elevation also had elevated zinc sulfate turbidity, the latter being usually depressed in liver parenchymal damage.

Urinary urobilinogen fails to reveal a difference between mild and marked liver cell damage because biliary obstruction reduces the urinary urobilinogen even in the presence of severe liver damage. The faulty take-up of urobilinogen from the portal circulation by the damaged liver cells, which results in increased urinary excretion of urobilinogen, cannot make itself felt in the absence of bilirubin from the intestine.[39] Urobilinogen was increased in eight of our patients.

A depression of serum albumin is said to indicate liver damage.[40] Two of our patients showed a depression of true serum albumin, 2.75 and 2.97 gm. per 100 cc. None of the Howe albumin tests were depressed, though 16 were elevated above 5 gm. per 100 cc.

Total serum protein concentration without albumin-globulin partition is no indicator of liver cell damage except when markedly decreased.[40] None of our patients showed a decrease of total protein, and two patients showed a slight elevation 8.13 and 8.32 gm. per 100 cc.

Protein-like material with properties of polypeptides or proteoses is found in plasma. The concentration of such materials in plasma rises markedly in patients with cancer and certain other diseases, but here again little is known of the source or significance of increased levels. The relation of these protein-like materials to the glycoproteins and mucoproteins of plasma is likewise in a state of considerable confusion.

Twelve of our patients showed an elevation above 4 mg. of tyrosine per 100 cc., and 12 patients showed a depression below 2 mg. of tyrosine per 100 cc.

Lichtman [43] states that tissues other than the liver are capable of cholesterol synthesis, that Beumer demonstrated that dogs fed on a cholesterol-free diet produced 30 times more cholesterol in a week than dogs fed on a normal diet, and that Thannhauser found an increase of total blood cholesterol after removal of the liver, although Mann and Bollman found no evidence of such a change in their reports. Lichtman [43] also points out that during hunger cholesterol decreases in the bile and increases in the blood. In liver damage the total cholesterol and its fatty and ester fraction are reduced. Lichtman [43] further states that experimental and clinical observations have pointed to the fact that the esterification of cholesterol takes place in the liver. In cases of liver damage the values for cholesterol ester are below those for free cholesterol, and in severer cases, as in acute yellow atrophy, the esters are depressed or absent. This is believed to be due to a disturbance in the liver of the synthesis of cholesterol esters from fatty acids and free cholesterol and of the hydrolysis of cholesterol esters into free cholesterol and fatty acids. This, in turn, is believed to be due to a disorder in ferments of liver cells disturbed in parenchymatous disease. Lichtman [43] also states that the value of the estimation of the cholesterol content of the blood and its ester fraction is enhanced by the correlation with bilirubin content of the blood, urine, and feces. Emphasis has been made on the parallel relationship between hypercholesterolemia and hyperbilirubinemia.

In our studies cholesterols, total and esterified, were elevated jointly in 19 patients. The total cholesterol was elevated alone in two patients, and cholesterol esters were elevated alone in three patients.

Elevation of the total van den Bergh test occurred jointly with elevation of total and esterified cholesterol in five patients and alone in one patient.

Of the two patients who showed an elevation of urinary bilirubin, both had normal total and esterified cholesterol values.

Lichtman [43] states that the liver is the principal tissue in the body serving not only for synthesis and supply of plasma phospholipids, but also for their removal. Twenty-three of our patients showed an elevation, and nine a depression, of serum lipid phosphorus.

Tests which have been observed to correlate significantly with liver cell damage, namely, the albumin-globulin ratio, cephalin flocculation, thymol turbidity, and sulfobromophthalein retention, and those of a less degree of correlation, namely, highly elevated serum bilirubin and slightly elevated alkaline phosphatase, did not occur in statistically significant numbers in our group of 53 multiple sclerosis patients. Furthermore, the joint occurrence of these tests was also not of statistically significant magnitude. With respect to total and esterified cholesterol values, which are said to be depressed below accepted normal standards in instances of liver cell damage, the abnormalities which occurred in our group of patients were elevated above the upper limits of normal in statistically significant numbers. The ratio of total to esterified cholesterol was normal in all of our patients. Cholesterol limits above the upper limits of normal occur in jaundiced patients, owing to reduced biliary excretion, provided other factors of hypercholesterolemia are excluded (e. g., hypothyroidism, pregnancy, nephrosis, and xanthomatosis). None of these conditions or jaundice was present in our patients. It is also held that there is a parallelism of diminished esterification of cholesterol and of abnormalities of serum and urinary bilirubin in liver cell damage. Such conditions did not exist in our patients. It is of interest that Fog [21] found no evidence of liver cell damage in liver biopsies in his group of multiple sclerosis patients.

It is known that lipids, in general, are concerned with the structure of the central nervous system, including myelin. The liver is concerned with the formation of plasma phospholipids and the esterification of plasma cholesterol. The frequent occurrence of hypercholesterolemia and increased phospholipid levels in multiple sclerosis should be further investigated in regard to the structural changes in the central nervous system.

SUMMARY AND CONCLUSIONS

Fifty-eight nonjaundiced patients with multiple sclerosis were tested with a group of 27 tests for evidence of hepatic dysfunction.

Tests which have been reported to have a significant statistical association with liver cell damage, namely, the albumin-globulin ratio, cephalin flocculation, thymol turbidity, and sulfobromophthalein retention tests, and those showing a less degree of correlation, namely, highly elevated serum bilirubin and slightly elevated alkaline phosphatase, did not occur in statistically significant numbers in our group of 58 patients. Furthermore, the joint occurrence of abnormalities in these particular tests was also not of statistically significant magnitude.

Total and esterified cholesterol levels, which are said to be depressed below accepted normal standards in instances of liver cell damage, were elevated above the upper limits of normal ranges in a statistically significant number of our patients. The ratio of total to esterified cholesterol was normal in all our patients. None of our patients, including those with high cholesterol levels, had jaundice or other clinical disorders associated with high serum cholesterol values.

Abnormalities of total cholesterol, cholesterol esters, lipid phosphorus, serum esterase, inorganic phosphorus, true globulin, Howe albumin, and zinc sulfate turbidity tests occurred with statistically significant frequency in the group of 58 patients studied. These abnormalities are not considered to be related to hepatic function.

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STUDIES ON HEADACHE

Cranial Artery Vasoconstriction and Muscle Contraction Headache

M. MARTIN TUNIS, M.D.
AND
HAROLD G. WOLFF, M.D.
NEW YORK

IT HAS been established * that some headaches arise from sustained contraction of skeletal muscle about the face, scalp, and neck. Conspicuous in this category are the recurrent headaches associated with feelings of tension, fatigue, and depression; many instances of recurrent "post-traumatic" headaches, and some of the headaches associated with arterial hypertension.

CLINICAL PHENOMENA TO BE INVESTIGATED

The muscle contraction headache is a steady, nonpulsatile ache. Additional descriptive terms include "tightness" bitemporally or at the occiput; "band-like" sensations about the head, which may become cap-like in distribution; "vise-like" ache; "weight," "pressure," "drawing," and "soreness." Distinct cramp-like sensations and a "feeling as if the neck and upper back were in a cast" are also described.

These head pains and other sensations occur frequently in the forehead and temples or in the back of the head and neck, but in other sites as well. They may be unilateral or bilateral, involving the temporal, occipital, parietal, or frontal regions, or all, and any combination. Commonly, there is pain on combing or brushing the hair or when putting on a hat. Although muscle contraction headache may be fleeting, with frequent changes in the site and intensity of recurrences, this is usually the type of headache which, localized in one region, may be sustained with varying intensity for weeks, months, and even years. The intensity of the headache may diminish by assuming certain individually favored positions. The patient may limit the motion of the head, neck, and jaws because it decreases his discomfort. There may be less discomfort when the head is supported by the hands.

Within the diffusely aching muscle tissues of the head, neck, and upper back there may be found on palpation one or many tender areas, or "nodules," which are sharply localized.

Pressure on contracted, tender muscles may augment headache intensity and may elicit tinnitus, vertigo, and lacrimation—features which also occur spontaneously. Such pressure on tender areas causes spread of the pain to adjacent portions of the head. Muscle contraction headache is aggravated by shivering from exposure to cold.

The headache associated with arterial hypertension is of two varieties. The first variety is primarily vascular in origin, and further consideration is not pertinent

From the New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College.

Present address: McGill University Clinic, Royal Victoria Hospital, Montreal, Canada (Dr. Tunis).

* References 1 through 4.

here. The second, due to muscle contraction, is nonpulsatile, usually in the nape of the neck and in the occiput. Sometimes the pain extends as high as the vertex and may be associated with neck rigidity, persistent torticollis, or elevation of the shoulders. The patient may complain that his head feels as though it were in a vise or that a steel band or tight cap were about the head (*douleur en casque*). These and other features of the headache are indistinguishable from those of muscle contraction in normotensive subjects.

The injection of 1% procaine hydrochloride into the involved tender tissues promptly reduces or eliminates pain arising from sustained contraction of skeletal muscle. Massage, comfortable warmth, the ingestion of moderate amounts of alcohol, or the intravenous administration of 0.5 gm. of amobarbital (Amytal) sodium may eliminate or reduce the intensity of the headache. However, the administration of ergotamine tartrate (0.5 mg. intramuscularly), an agent which constricts cranial arteries, fails to relieve, and often aggravates, the headache. Also carotid artery compression on the side of the headache usually augments the intensity of the head pain.

The latter observations suggested that a diminution of the blood supply to the painfully contracted muscles might be a factor in the production of the headache. In keeping with this view, it was indicated in preliminary experiments from cranial artery pulse wave records that relative vasodilatation as well as muscle relaxation accompanied procedures which eliminated or reduced the intensity of the head pain. Accordingly, experiments were undertaken to investigate cranial artery function in subjects with muscle contraction headaches.

METHOD

Muscle action potentials were recorded on an eight-lead Grass electroencephalograph. Six needle electrodes, made with #26 hypodermic needles to minimize discomfort, were inserted bilaterally into the scalp in the frontal, temporal, and occipital regions. Two disc electrodes were placed bilaterally on the skin over the muscles at the back of the neck. The ear lobe was used as the neutral electrode for records from muscle in any one site.

Glycerin pellotes† (a glycerin-filled rubber sphere affixed to an airtight metal holder with an escape valve) were placed bilaterally on the skin over selected cranial arteries to "pick up" the pulsations. Pulse wave tracings[6] were obtained by connecting the pellote through a rubber tube and a piesoelectric crystal "pick-up" to a multiple-channel direct-writing recorder.‡

The following nutrient arteries were examined in this study: (1) the supraorbital artery, which supplies the frontalis muscle and the integument and pericranium of the forehead; (2) the frontal branch of the superficial temporal artery, which supplies the temporalis muscle and the integument and pericranium of the temporal region; (3) the occipital artery, which gives off large branches to the occipitalis, trapezius, longissimus capitis, splenius, stylohyoid, and digastric muscles.[5]

A group of 20 normotensive and 6 hypertensive subjects who had recurrent headaches were studied during 85 headache episodes, as well as during their headache-free intervals. Four to 30 series of cranial artery pulse wave records were obtained at variable intervals during a 6- to 12-week period from each subject. A total of 254 series of pulse wave records were thus assembled, indicating the cranial artery function of these subjects during headache as well as when headache-free. Simultaneous bilateral electromyograms were obtained from the frontal, temporal, and occipital muscles and the posterior nuchal muscles, during at least one headache

† Cambridge Instrument Co., Inc.

‡ Sanborn Company.

in each subject. During the observation period of one to three hours, records were made during the spontaneous onset, subsidence, and recurrence of headache in the same or a different site. Records were obtained from several subjects during three to four such recurrences of headache. Five subjects were studied during two separate headache episodes. One of these subjects, a patient with hypertension, experienced 12 separate headache attacks during three and one-half hours on the first occasion and 10 such attacks during the second observation period, one week later.

Although pulse wave records from the supraorbital, temporal, and occipital arteries (both right and left) and simultaneous electromyograms from the muscles supplied by these vessels were obtained, for brevity, observations from the right temporal region during headache and during headache-free intervals are reported below. Pulse wave records from other arteries differed in no essential way from those of the right temporal artery when taken under comparable circumstances of headache and skeletal muscle contraction.

The change in muscle action potential was expressed in terms of the increase in amplitude of the stylus deflections during headache, as compared with the amplitude of those recorded during headache-free intervals. Owing to the limitations of the equipment, quantitation of the frequency change was impractical. The change in muscle action potential and, presumably, the degree of muscle contraction was therefore expressed in terms of the increased amplitude of the stylus deflections. An arbitrary unit of 1 was assigned to the mean amplitude of 50 consecutive

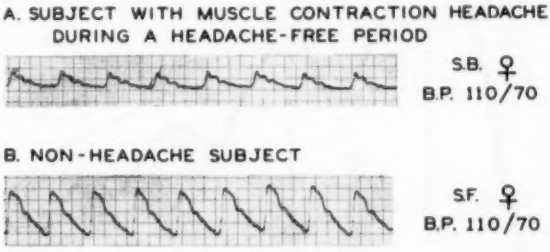

Fig. 1.—Comparison of right temporal artery pulse wave contours in two subjects.

deflections on the action potential record, selected because of maximum height during a headache-free period. The mean of 50 consecutive deflections from the record during headache, again selected at maximum height, was compared with the latter.

OBSERVATIONS

SERIES I.—*Comparison of right temporal artery pulse wave contours of a nonheadache subject with those of a headache subject during a headache-free period.*

Representative segments from the right temporal artery pulse wave records of a muscle headache subject during a headache-free interval (upper tracing) and of a nonheadache subject (lower tracing) are reproduced in Figure 1. A small-amplitude wave with one or more well-defined reflected waves was usual on the records from the headache subjects. By contrast, on records from nonheadache subjects the pulse wave amplitude was greater and the contour was "smoother"; i. e., there were fewer or no reflected waves.

SERIES II.—*Comparison of measurements of right temporal artery pulse wave contours* (a) *from nonheadache subjects,* (b) *from headache subjects when headache-free, and* (c) *from headache subjects during right temporal muscle contraction headache.*

Records obtained from the frontal branch of the right temporal artery of 10 "headache" subjects at the midpoint of a headache-free interval of not less than 48 hours' duration were selected for measurement and analysis.

Also for purposes of comparison, six to eight records were obtained from the frontal branch of the right temporal artery from 10 subjects who seldom or never had headache and who did not have headache during a three-month period of study. A total of 72 records were thus obtained. In this nonheadache group the earlier records differed in no way from those obtained subsequently.

All the subjects whose records were selected had stable brachial artery blood pressures (110/70 to 120/80) and pulse rates (70 to 76 per minute).

One hundred consecutive right temporal artery pulse waves from the record of each subject were measured, and the data from the headache-free muscle headache subjects were compared with those from the nonheadache group. Further, the data

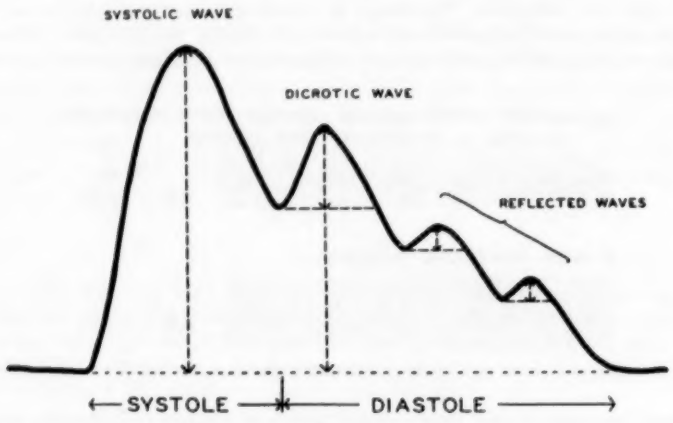

Fig. 2.—Arterial pulse wave contour.

from the headache-free subjects were compared with those from the same subjects during right temporal headaches in which simultaneous electromyograms from the area of head pain evidenced increased muscle contraction.

The components of the cranial artery pulse waves as shown in Figure 2 were measured as follows: (1) the height, in millimeters of the apex of the systolic component of the pulse wave from the base line; (2) the height, in millimeters, of the apex of the dicrotic wave from the pulse wave base line; (3) the height, in millimeters, of the apex of the dicrotic wave from its own base line; (4) the number of reflected waves on the descending limb of the base line, and (5) the sum of the amplitudes of these reflected waves.

Changes in the amplitude of the arterial pulse waves (systolic apex to base) were taken as evidence of changes in the caliber of the artery.[6] Inferences were made concerning the contractile state of the frontal branch of the right temporal artery on the basis of these changes in conjunction with changes in the measured components of the pulse wave.[6]

The range, the average, and the standard deviation of the measurements of 1,000 pulse wave contours from subjects in three categories are shown in the Table: (1) from 10 nonheadache subjects; (2) from 10 headache subjects when headache-free, and (3) from 10 headache subjects during headache from contraction of the right temporal muscle.

The average pulse wave amplitude (systole) from records of the headache subjects when headache-free was significantly less than the average of comparable measurements from the nonheadache group. Thus, for the nonheadache group this average amplitude was 12 mm., with a standard deviation of + 0.95 mm., as contrasted with a mean amplitude of 8.3 mm. (S. D. ±2.6 mm.) for the headache group

*Analysis of Pulse Wave Contours**

	Headache Subjects		
	During Headache	Free of Headache	Nonheadache Subjects
Systoles			
Wave amplitude, mm.			
Range	2-9	5-16	8-17
Average	4.6	8.3	12
Standard deviation	± 1.9	± 2.6	± 0.95
Dicrotic waves			
Apex to base, mm.			
Range	1-7	2-8	1-12
Average	2.9	4.7	6
Standard deviation	± 1.5	± 2.0	± 0.7
Wave amplitude, mm.			
Range	0-4	0-5	0-3
Average	1.4	1.2	1.2
Standard deviation	± 1.2	± 0.9	± 0.5
Diastoles			
Number of reflected waves			
Range	0-5	0-3	0-2
Average	1.5	1.2	0.6
Standard deviation	± 1.3	± 0.8	± 0.5
Size of reflected waves, mm.			
Range	0-9	0-8	0.1-1
Average	1.9	1.0	0.4
Standard deviation	± 1.5	± 1.1	± 0.4

* One hundred consecutive waves from each of 10 subjects who have muscle contraction headaches versus 10 subjects who never have headaches.

when headache-free. Further, the average number and amplitude of the reflected waves in the headache group significantly exceeded these measurements in the nonheadache group. In the latter group the mean number of reflected waves was 0.6 (S.D. ± 0.5), and the mean amplitude was 0.4 mm. (S.D. ± 0.4 mm.), as compared with a mean of 1.2 (S.D. ± 0.8) reflected waves and an average amplitude of 1.0 mm. (S.D. ±1.1 mm.) in the headache group when headache-free.

During headache the mean pulse wave amplitude (systole) was 4.6 mm. (S.D. ± 1.9 mm.), as compared with a mean amplitude of 8.3 mm. (S.D. ± 2.6 mm.) for these same subjects when headache-free.

Simultaneous electromyograms from skeletal muscle involved in headache in the right temple were obtained as described above. In all instances the frequency and amplitude of the stylus deflections were increased. As compared with an arbitrary

unit of 1 assigned to the average amplitude of the action potential record during a headache-free period, there was a tenfold increase of potentials from the right temporal muscle during headache.

Comment.—These facts indicate that even in subjects when headache-free the caliber of the frontal branch of the right temporal artery was significantly less in the headache subjects (mean amplitude 8.3 mm.) than in the nonheadache group (mean amplitude 12 mm.). Also in contrast to the nonheadache subjects, relative temporal artery constriction was evidenced among the headache group by the increased number (1.2 vs. 0.6) and amplitude (1.0 mm. vs. 0.4 mm.) of the reflected waves.

During headache associated with contraction of the right temporal skeletal muscle, increased constriction of the right temporal artery was indicated by the mean amplitude of 4.6 mm., as contrasted with a mean of 8.3 mm. for these same subjects when headache-free.

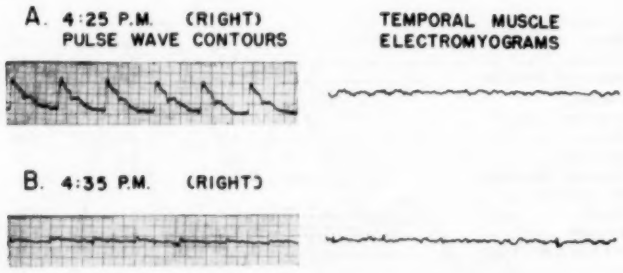

Fig. 3.—Spontaneous temporal artery constriction without muscle contraction or headache.

During such right temporal muscle contraction headache, also, there was a tenfold increase of the average amplitude of action potential from muscles in the right temporal region as compared with records during headache-free periods.

Thus, during headache in the right temporal region, pulse wave records from the right temporal artery evidenced vasoconstriction, and simultaneous electromyograms from the right temporal muscle evidenced increased muscle contraction. It is inferred that head pain arose from sustained contraction of ischemic muscle.

SERIES III.—*Right temporal artery vasoconstriction without headache.*

The records in Figure 3 show spontaneous right temporal artery constriction (Fig. 3*B*). Simultaneous electromyograms from the right temporal muscle do not show increased muscle action potentials. This record was not associated with headache, and others like it were often obtained from muscle headache subjects during headache-free periods.

Comment.—Right temporal artery constriction for short intervals was frequently demonstrated in the absence of headache. However, when long sustained, such constriction was usually accompanied by a variety of disagreeable head sensations.

SERIES IV.—*Right temporal muscle contraction without headache.*

Records indicating increased muscle action potentials bilaterally in the frontotemporal regions were obtained when briefly frowning and clenching the jaw. Such

short-lived contractions did not result in headache. The spontaneous occurrence of such increased muscle contractions in the absence of headache was also frequently observed. In Figure 4 the left temporal myogram shows markedly increased muscle action potential when compared with the record from the right side. There was

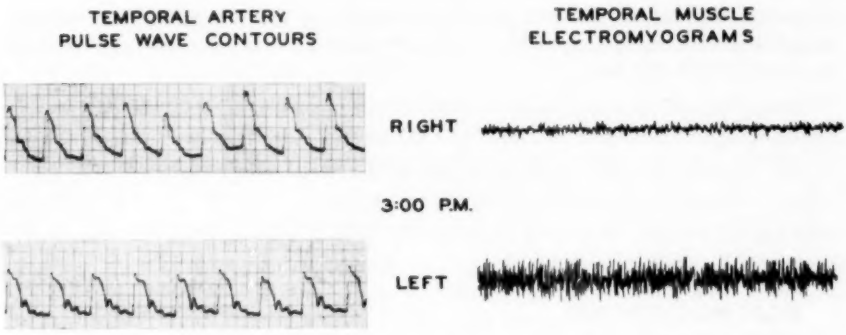

Fig. 4.—Spontaneous and short-lived temporal muscle contractions without vasoconstriction or headache.

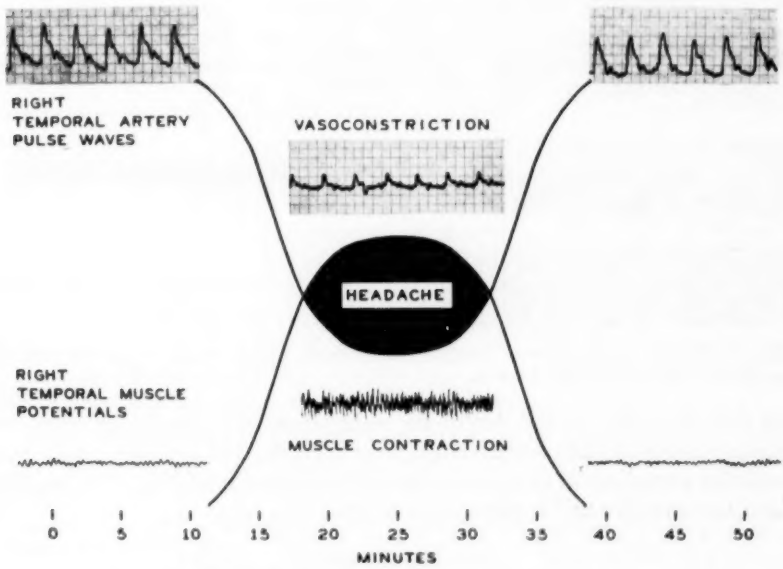

Fig. 5.—Muscle contraction headache, right temporal region.

minor vasoconstriction in the pulse wave records from the left temporal artery. No headache was experienced.

Comment.—In the above, increased contraction of temporal skeletal muscle for short periods was not associated with headache. However, when long sustained, such contractions were usually associated with disagreeable head sensations or even headache.

SERIES V.—*Concurrent right temporal artery constriction; right temporal muscle contractions, and headache, in a normotensive subject.*

In Figure 5 records obtained prior to, during, and after termination of spontaneous right temporal muscle contraction headache are reproduced. Evident are the definite temporal artery constriction and increased muscle action potential, simultaneously recorded in the area of head pain during the headache. The records obtained after termination of the headache were almost identical with records obtained prior to its onset.

SERIES VI.—*Concurrent right temporal artery constriction, right temporal muscle contractions, and headache in a subject with arterial hypertension.*

The records obtained from a subject with arterial hypertension during right temporal muscle contraction headache are reproduced in Figure 6. During the headache, right temporal muscle action potentials were strikingly increased, and at the

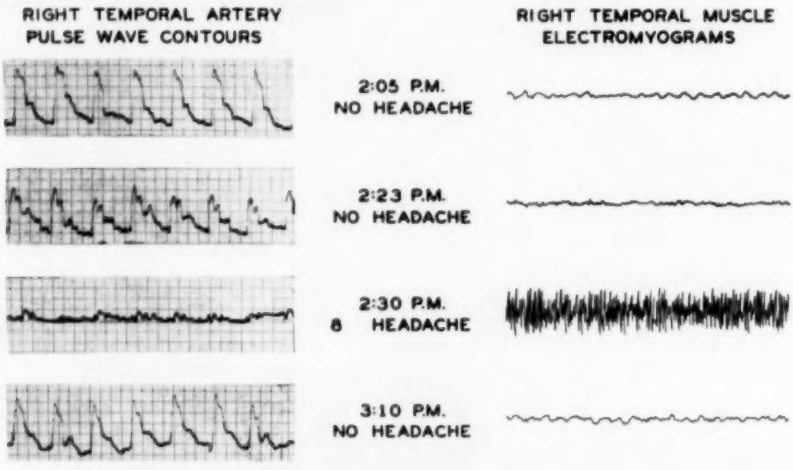

Fig. 6.—Simultaneous pulse waves and electromyograms during muscle contraction headache in a subject with arterial hypertension.

same time there was constriction of the right temporal artery. Also, there was beginning vasoconstriction seven minutes prior to the onset of headache. Such vasoconstriction preceding the onset of muscle contraction and headache was often noted in both normotensive and hypertensive subjects.

GENERAL COMMENT

These studies show that concurrent constriction of nutrient arteries and increased muscle contraction result in headache. Evidence supporting the view that sustained muscle contraction can cause headache was presented some years ago.§ It was then suggested that muscle contraction, reflexly induced and secondary to noxious stimulation, could in part explain the headaches associated with diseases of the eyes, the teeth, the nose, the paranasal spaces, the cervical vertebrae, and, as well, the

§ References 1 through 3.

headaches associated with prolonged vascular distention. When these observations were made, it was not ascertained whether there was concurrent reduction of the blood supply of the involved muscles, although it seemed likely; and the suggestion was made that sustained contraction of muscle, if forceful enough, could in itself interfere with proper oxygenation of the muscle and thus contribute to pain production. It was not considered necessary to assume that vasoconstriction of the relevant nutrient arteries to the muscles was essential to the genesis of the pain. This formulation is still tenable despite the new facts presented in this study.

In short, sustained skeletal muscle contraction in itself, if sufficiently forceful and sustained, can be painful. However, if in addition there is vasoconstriction of the relevant nutrient arteries, the amount and duration of skeletal muscle contraction necessary for pain production need be far less, and the intensity of the resultant pain from muscle contraction may be greater. It is likely that the large group of normotensive and hypertensive persons with headaches associated with emotional conflict, tension, and contraction of the cranial and cervical muscles are those most likely to exhibit the combination of muscle contraction and vasoconstriction. Again, however, it is unnecessary to assume that both factors must always be present to induce headache.

SUMMARY AND CONCLUSIONS

Bilateral pulse waves were recorded from the supraorbital, temporal, and occipital arteries of 20 normotensive and 6 hypertensive subjects during 85 headache episodes and during headache-free intervals. Measurements of 1,000 right temporal artery pulse wave contours from records of 10 of these headache subjects, both during headache and in headache-free periods, were compared with a similar number of right temporal artery pulse wave contour measurements from 10 nonheadache subjects.

Simultaneous with the recording of pulse waves, electromyograms from skeletal muscle about the cranium supplied by these vessels were also obtained. Also, electromyograms from the 10 headache subjects when headache-free were compared with those obtained from the same subjects during headache.

By comparison with the records of nonheadache subjects, pulse wave records from headache subjects indicated relative vasoconstriction even during headache-free intervals, as revealed by the significantly smaller mean amplitude of the pulse wave contour and the greater size and number of reflected waves.

Right temporal artery pulse wave records from 10 headache subjects during right temporal muscle contraction headache exhibited greater vasoconstriction than did records from these same subjects when headache-free. Moreover, during such headache there was a tenfold increase in amplitude of action potentials from the involved temporal muscle.

Neither short-lived temporal artery constriction, alone, nor brief contraction of temporal muscle alone resulted in headache. When long sustained, muscle contraction alone or cranial artery constriction, *per se*, sometimes resulted in disagreeable head sensations or pain. The concurrence of the two more commonly resulted in headache. Indeed, sustained contraction of skeletal muscle and constriction of its nutrient artery were often concurrent in certain subjects and resulted in muscle contraction headache. This correlation was noted in normotensive as well as in hypertensive subjects.

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POLIOMYELITIS

IX. The Cerebral Hemispheres

A. B. BAKER, M.D.
SAM CORNWELL, Ph.D.
AND
FAE TICHY, M.D.
MINNEAPOLIS

MOST STUDIES on poliomyelitis seem to suggest that this disease is not limited to the spinal cord but often involves the entire nervous system; however, the degree and the nature of the involvement within the cerebral hemispheres, particularly within the cerebral cortex, have never been studied in detail in a large series of cases. It was felt that such a study in 75 fatal cases might be of value in determining the extent to which the virus of poliomyelitis involves the cerebral cortex and in explaining many of the clinical symptoms and signs of this disease which apparently are not spinal in origin.

Strümpell [1] in 1884 first described a form of cerebral paralysis in children which he felt was a cerebral form of poliomyelitis. The illness was acute in onset, associated with fever, vomiting, convulsions, and coma. The children remained unconscious for days and often manifested paralysis of an upper motor neuron type. Many of the patients developed permanent residuals in the form of seizures, athetosis, speech disturbances, and mental defects. The author felt that this illness was identical with poliomyelitis except that the latter affected the motor cells of the spinal cord, while the former affected the cells of the cortex. He suggested the term polioencephalitis for this condition.

Médin [2] in 1896 observed three cases of spastic paralysis occurring in children during a Stockholm epidemic. He felt that Strümpell's contention was correct and that this type of paralysis could follow poliomyelitis. Subsequently, a number of investigators have reported cases of combined flaccid and spastic paralyses in poliomyelitis, thus suggesting that the spastic hemiplegia of Strümpell may actually have been the result of this disease (Williams,[3] Neurath,[4] von Kiss and Fényes [5]).

The relationship of Strümpell's cases to poliomyelitis has been questioned by many subsequent investigators (Barker,[6] Wickman,[7] and Rothman [8]). All agreed that poliomyelitis may cause encephalitic changes but doubted the occurrence of a true hemiplegia. Wickman [7] reported that in hundreds of cases examined during the Swedish epidemics, there were no cases of spastic hemiplegia. Heine [9] had similar experiences with his cases and, therefore, refused to accept Strümpell's infantile hemiplegia as a form of poliomyelitis. Rothman [8] also made extensive studies and agreed with Heine that they were separate conditions. In a large series of epidemic

From the Division of Neurology, University of Minnesota Medical School.

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cases of poliomyelitis he failed to observe a single case of Strümpell's hemiplegia. In the American epidemics of poliomyelitis, cerebral involvement has often been reported, but cases of spastic hemiplegia have not occurred (Fischer and Stillerman [10]; Steinhardt [11]; Koplik [12]; Baker, Matzke, and Brown [13]).

The question may be raised as to whether there is a true cerebral form of poliomyelitis. Most investigators feel that the virus does selectively involve the cerebral cortex but that the damage is never severe enough to produce a spastic hemiplegia, although hyperactive reflexes and the positive toe signs may result (Pette,[14] Demme,[15] and Környey [16]). Generally the clinical manifestations of polioencephalitis are those of a diffuse involvement and occur in pure form in about 2% of cases of poliomyelitis (Koplik [12]; Steinhardt [11]; Fischer and Stillerman [10]; Weber and Schmid [17]; Windorfer [18]; Hyland and associates [19]). Headache is a cardinal symptom and is often associated with mild fever, back pain, stiff neck, and nausea and vomiting. The temperature rises rapidly and the patient becomes apprehensive, fretful, restless, and irritable. These symptoms may recede or may be followed by lassitude, drowsiness, and/or apathy. The drowsiness may be followed by a state of stupor. During the height of the illness there may be periods of confusion, convulsions, or even coma (Hyland and associates [19]; Weber and Schmid [17]). The neurological findings are most variable. The deep reflexes are often hyperactive but may be unequal, or even reduced. The toe signs may be positive. Motor weakness, if present, is generally of the lower motor neuron type.

Fanconi and his associates [20] reported 375 cases of poliomyelitis, in which 37 showed definite cerebral symptoms. Involvement of the sensorium occurred in 27 and consisted of somnolence or complete stupor. Convulsions were present in 9 cases, pyramidal signs in 11 (although none showed a spastic hemiplegia), extrapyramidal symptoms in 6, and cerebellar symptoms in 12. The mortality rate was 10%. Denys and Dereymaiker [21] reported 23 cases of poliomyelitis, in which 6 had encephalitis. Of these, alterations of sensorium occurred in five, convulsions in two, and pyramidal symptoms in three.

Although the lesions in poliomyelitis tend to be much severer and more frequent within the spinal cord, changes of a similar nature can also occur within the cerebral cortex. As early as 1907 Harbitz and Scheel [22] studied the brain in 17 cases of poliomyelitis and observed large inflammatory infiltrations along the Sylvian fissure, involving the temporal and frontal lobes, as well as some invasion of the cortex of the central gyri with degeneration of the ganglion cells. In 1910 Wickman [7] reported histologic changes within the motor cortex, the occipital area, the temporal area, and the cerebellum in four cases of poliomyelitis. Stadler [23] observed cerebral changes in 9% of his cases, while Lemmon [24] reported involvement in 34% of 49 patients.

The selectivity of poliomyelitis to the motor cortex was first suggested by Thomas and Lhermitte [25] and later substantiated by Spielmeyer,[26] Stiefler and Schenk,[27] Peters,[28] Swan,[29] and Howe and Bodian.[30] André-Thomas and Lhermitte examined only scattered areas of the frontal and parietal cortex of a single case of poliomyelitis. They found changes chiefly in the motor cortex, implicating the Betz cells, and concluded that poliomyelitis was a disease of the motor system. Horányi-Hechst [31] recorded one of the most complete studies of the cerebral pathology in this disease. Of his 38 cases, 24 showed cerebral alterations, chiefly of an interstitial type limited primarily to the precentral cortex. Many of the nerve cells revealed typical acute changes. In 17 cases the white matter showed inflammatory alterations. Glial nodules

and inflammatory exudates were observed in the molecular layer of the cerebellum, the basal nuclei, the claustrum, and the hypothalamus. Peters [28] observed histologic alterations within the brain in all his 39 fatal cases of poliomyelitis. The inflammatory reaction within the brain often surpassed that in the spinal cord. Only the frontal, temporal, and occipital poles showed no intense inflammatory reaction. The most striking neuronal changes occurred in the region of the large nerve cells of the motor and prefrontal cortex. Swan,[29] in a study of eight cases, described neuronal alterations in the precentral gyrus of all but one patient. Howe and Bodian [30] studied 13 human cases and in 12 found lesions consisting of perivascular cuffing, neuronophagia, and focal mesodermal-glial infiltrations scattered throughout Area 4. Two cases showed a few lesions in Area 6; four cases, lesions in Area 1; two cases, infrequent lesions in the frontal cortex, and one case, occasional lesions as far rostral as the orbital gyri.

Not only do the pathologic lesions in poliomyelitis appear to be localized to the motor cortex, but they also seem to implicate certain layers within the motor area. Such a layer specificity was first suggested by Spielmeyer,[20] who found the neuronal alterations within the motor area limited primarily to the third layer. The inflammatory foci did not show this specificity but were scattered throughout the motor cortex.

Környey [16] also emphasized the laminal electivity of the lesions. In all eight cases that he studied, the nerve cell changes were limited to the upper third of the central gyrus, involving primarily the giant pyramidal cells of Layers 3 and 5. Stiefler and Schenk [27] reported similar findings in 7 out of 12 cases that they studied.

The pathologic changes observed in the hemispheres of man have been reproduced in the experimental disease in monkeys. Hurst [32] studied the cerebral changes after intracerebral inoculations of the poliomyelitis virus in monkeys. He observed foci of inflammation scattered throughout the gray matter, with extension into the subjacent white matter. The frontal and occipital poles were uninvolved. Nerve cell damage was mild and limited to the motor cortex. Pette [14] inoculated his animals by different routes, but the cerebral changes were similar. There was a predilection of lesions for the precentral gyrus, with the lesions limited to the third and fifth cortical layers. Often there were only collections of inflammatory elements, with the nerve cells remaining intact.

PRESENT INVESTIGATION

The entire brain was studied in 75 fatal cases of bulbar poliomyelitis. In all these cases the changes within the medulla, pons, midbrain, and hypothalamus had already been investigated and were available for comparison with the alterations found within the cerebral cortex and white matter (Baker, Matzke, and Brown [13]; Matzke and Baker [33]; Matzke and Baker [34]; Baker, Cornwell, and Brown [35]). Blocks were taken from the following areas in each case: hippocampus, corpus cinguli, corpus callosum, inferior frontal gyrus, prefrontal area, superior precentral gyrus, inferior precentral area, postcentral gyrus, superior parietal gyrus, inferior parietal gyrus, superior temporal gyrus, transverse temporal gyrus, inferior temporal gyrus, lateral occipital gyrus, and the calcarine gyrus. Sections from all areas were prepared with the Nissl stain, the hematoxylin-eosin stain, and Weil's stain. Three types of histopathologic changes were observed within the cerebral hemispheres: (1) a meningeal inflammation, (2) a diffuse and/or focal interstitial cell reaction, and (3) neuronal damage. In most cases all changes occurred in varying degrees of severity. However, for the sake of simplicity they will be discussed separately.

Meningeal Involvement

The histologic feature of the meningeal reaction in poliomyelitis has received a great deal of study and has been reviewed in detail by us in a previous publication (Baker [36]). However, there still remains a number of problems related to this meningeal reaction which warrant clarification, such as (1) the frequency of cerebral meningitis in unselected cases of bulbar poliomyelitis, (2) the relative intensity of this meningeal reaction in the various regions of the brain, (3) the relationship of the meningitis to the interstitial cell reaction within the cerebral cortex and white matter, and (4) the relationship of the meningitis to the underlying neuronal changes.

Inflammatory changes in the leptomeninges over the cerebral hemispheres were observed in 85% of our cases. These changes consisted of a mild to moderate exudation of round cells, mostly lymphocytes in most cases, but with a slight preponderance of polymorphonuclear leucocytes in the rare very acute case. A few scattered

Table 1.—*Number of Cases Showing Meningitis, Encephalitis, and Neuron Damage in Seventy-Five Unselected Cases of Bulbar Poliomyelitis*

Area of Brain	Meningitis With or Without Other Pathology	Meningitis Plus Encephalitis	Meningitis Plus Encephalitis and Neuron Damage	Encephalitis but No Meningitis	Neuron Damage but No Meningitis	Encephalitis and Neuron Damage but No Meningitis
Hippocampus	28	12	2	6	..	..
Gyrus cinguli and corpus callosum	11	6	..	2	..	..
Inferior frontal	15	5	2	3	1	..
Prefrontal	24	7	5	3	2	..
Superior precentral	53	47	39	..	2	17
Inferior precentral and postcentral	6	6	6	5	..	4
Superior parietal	11	..	2	2	..	..
Inferior parietal	9	2	2	2	5	..
Superior and transverse temporal	9	..	..	2	..	3
Inferior temporal	15	..	2	2	..	..
Lateral occipital	6	2	..	2	2	..
Calcarine	6	2	..	..	..	..

erythrocytes were occasionally present in the subarachnoid space. Macrophages were observed in most cases and often contained phagocytosed debris or brownish pigment. Some of the lymphocytes appeared to be in transitional stages resembling the mature plasma cell. The meningeal reaction usually extended into the sulci and fissures and occasionally could be followed as perivascular cuffing into the underlying cortex.

All regions of the brain were at least occasionally implicated by this meningeal reaction; however, the posterior portions of the frontal lobes were by far the most commonly involved (Table 1). Specifically, the precentral areas were most frequently implicated, showing a meningeal reaction in 53 or 70% of our 75 cases. The next most frequently involved areas were the hippocampus and prefrontal gyri, which showed meningeal changes in 28 and 24 of the cases, respectively. The inferior temporal and inferior frontal gyri were implicated in only 15 of the cases. The occipital lobe was most infrequently involved and contained the slightest degree of meningeal reaction, being implicated in but six cases. It is readily apparent from a survey of these changes (Table 1) that the most intense and most frequently involved areas of meningitis were localized to the vicinity of the motor cortex. These observations are of great interest when compared with the neuronal alterations.

In most of the cases the meningeal involvement was mild and diffuse and bore little correlation to the inflammatory or neuronal changes within the underlying brain tissue (Table 1). Encephalitic pathology was associated with the meningitis in less than one-half the cases in all the locations studied except the precentral and postcentral gyri. In the superior precentral gyrus, of 53 cases with meningitis, 47, or 90%, had an associated interstitial cell reaction within the cortex, and 26, or 50%, showed underlying neuronal changes. In 17 cases there was no evidence of meningitis, but fairly extensive inflammatory or neuronal changes within the brain tissue.

Our studies would indicate that many areas show minimal meningitis without any associated cerebral pathology; however, whenever there is a relatively intense cerebral involvement (either inflammatory or neuronal), the meninges will usually demonstrate some associated changes. These observations would seem to suggest that the extension of the tissue changes is most likely from the cortex to the meninges, rather than being initiated within the meninges and extending inward.

Comment.—Some of the earliest studies on poliomyelitis have suggested that this disease may selectively implicate the meninges, producing a meningeal type of poliomyelitis (Jelliffe,[37] Wieland,[38] Netter [39]). These patients develop headaches, nausea, pain in the neck and back, stiffness of the neck, rigidity of the back muscles, opisthotonos, Kernig's sign, tonic or clonic movements, somnolence, and even coma. This form may recede rapidly without any motor weakness or residuals. It has also been felt that some degree of meningitis always precedes in those cases which later develop motor involvement. The majority of the earlier investigators have, therefore, postulated a meningeal spread of the disease. Harbitz and Scheel,[22] for example, in a study of 11 cases, found most of the cortical changes to be inflammatory and situated in those gyri adjacent to the Sylvian fissures and the central gyri, where the pia was most severely involved. In the basal ganglia, the most marked lesions occurred in the posterior end of the thalamus, where the inflammation could spread inward from the base along the vessels of the anterior and posterior perforated spaces. Wickman [7] and Marinesco and associates [40] have taken a similar view. Wickman, who first emphasized the meningeal form of poliomyelitis, described active cerebral meningitis in four cases, and in each there were some inflammatory changes in the cortex immediately subjacent to the active meningitis. Marinesco and his co-workers found a cerebral meningitis in 6 out of 280 cases of poliomyelitis. This meningeal involvement was severest along the base of the brain and in the interpeduncular regions and appeared to extend along the perivascular spaces into the cortex. Inflammatory nodules were not seen in the brain except in the region of an active meningitis.

More recent studies have questioned the importance of the meningeal spread of poliomyelitis, and many of the more comprehensive experimental studies have shown a definite independence between the cerebral and meningeal lesions (Horányi-Hechst,[31] Fairbrother and Hurst [41]). Horányi-Hechst in his 38 fatal cases found the meninges of the cortex always mildly involved. Over the cortex the cellular reaction was irregular, being present in some areas and absent in others. There was no correlation between parenchymal changes and meningeal reaction. In many cases with meningeal reaction there were no alterations in the parenchyma, either inflammatory or neuronal. Fairbrother and Hurst, in experimental studies on the monkey, observed deep cortical foci and perivascular areas of inflammation which were

entirely independent of any meningeal reaction. They felt that these lesions resulted from transmission of the disease along the nerve fibers and that this mode of spread was the primary one, although some meningeal spread may also occur.

Our studies seem to indicate that although the cerebral cortex may be implicated secondary to a meningitis in poliomyelitis, this is by no means the only, or even the predominant, method of cortical involvement. This fact is particularly emphasized by the large number of cases that show a fairly extensive cortical involvement, both inflammatory and neuronal, without any evidence of a meningitis. It is apparent that there must be some other source for these cortical lesions, such as a spread along the nerve fibers or even a spread through the vascular system.

Neuronal Alterations

Normal Structure.—The normal architecture of the cerebral cortex has been well documented. It might be well, however, to summarize briefly the normal appearance of those cortical areas selected by us for study in order to describe the criteria which we used for cell damage.

1. Hippocampus: This block contained a cross section of structures in the tip of the temporal lobe, including the dentate and hippocampal gyri and the neighboring areas of the cerebral cortex, the temporal horn of the lateral ventricle, and the hippocampus proper. The cortex of the various gyri seen in this section has a uniform appearance. It is moderately thick and is not easily separable into layers. The most superficial layer is relatively neuron-free (the plexiform or molecular layer), being composed of neuropil with occasional pyramidal cells, some horizontally deployed. The characteristic cells through all deeper layers are of pyramidal shape and are oriented, mostly, perpendicular to the surface. They are mostly of the "medium-size" type, with occasional small pyramidal cells in the outer layers. These medium-sized pyramidal cells, like the same cell type in other cortical areas, are well-defined angular cells with distinct cell and nuclear membranes, moderately fine Nissl granulation, and central round nuclei. The hippocampus itself, lying near the ventricle, contains closely packed oval-shaped cells (about three to four cells thick but not layered) with moderately fine Nissl granules and a central round nucleus.

2. Gyrus Cinguli: This cortex is of the premotor frontal type. It is moderately thick and contains all six layers with reasonably clear differentiation, except for the internal granular Layer 4 which is not easily separable, though cells of the stellate or granular type are present in somewhat increased concentration at the junction of Layers 3 and 5. The plexiform Layer 1 is relatively thick. Layer 2 contains small pyramidal cells with indistinct Nissl granules and a central nucleus, as well as granular cells. These latter are small, irregular, round, oval, or stellate cells with a central nucleus, fine Nissl granules, and poorly defined membranes. Layer 3, not sharply separated from Layer 2, contains mainly medium-sized pyramidal cells, which increase in size in the deeper portion. These cells have sharp contours and angles, moderately coarse Nissl granules, and a central nucleus. Layer 4 is not a distinct layer but does contain small stellate cells with short pointed processes and poorly defined boundaries, as well as small and medium-sized pyramidal cells. Layer 5 contains medium and large pyramidal cells. The large ones have coarser, more angular Nissl granules, regular triangular outline, and a central nucleus. Layer 6 contains spindle cells arranged in both horizontal and vertical planes. These

cells contain a variable number of fine Nissl granules and occasional coarser granules, and a central oval nucleus. Some medium pyramidal cells and stellate cells are also present in this layer.

3. Inferior Frontal Gyrus: This cortex is similar to the cingulate gyrus, but is somewhat thinner and has a more distinct internal granular Layer 4 with more stellate or granule cells. The cell distribution in the layers is also the same except for more small pyramidal cells in superficial Layer 2 and fewer medium pyramidal cells in Layer 3. There are also more spindle cells in Layer 6.

4. Prefrontal Gyrus: The cortex here is similar to the inferior frontal cortex, but with a thicker internal granular Layer 4 (more stellate cells in it), increased number of small pyramidal cells and stellate cells in Layer 2, and thicker Layers 5 and 6 with more medium and large pyramidal cells in Layer 5 and more spindle cells in Layer 6.

5. Precentral Gyrus: This cortex is of the typical motor type with very numerous pyramidal cells in Layers 2, 3, and especially 5; scattered giant pyramidal cells in Layer 5, and a thick Layer 6 with many spindle and pyramidal cells. Layer 4 is almost nonexistent, though a scattering of stellate or granular cells is present at the vague line of junction of Layers 3 and 5. Layer 5 is particularly thick and cell-rich. The relatively acellular Layer 1 (plexiform or molecular layer) is relatively thin.

6. Postcentral Gyrus: This cortex is relatively thick but has fewer large and medium pyramidal cells, thinner Layers 5 and 6, slightly thinner Layers 2 and 3, with fewer cells in both, and a thick, well-marked Layer 4, with numerous stellate cells.

7. Superior and Inferior Parietal Gyrus: The cortex here is of the sensory type, similar to the postcentral gyrus. The cortex is relatively thin, especially the supragranular Layers 2 and 3. Layer 1 is of average thickness, with few cells. Layers 2 and 3 are moderately thin and have few pyramidal cells (mostly of medium size) and more stellate or granular cells (particularly in the superficial portion of Layer 2). Layer 4 is thick and contains numerous stellate or granular cells. Layers 5 and 6 are relatively thin; large pyramidal cells are sparse in Layer 5, the division between Layers 5 and 6 is indistinct, and the cells of Layer 6 are mainly spindle cells.

8. Superior and Transverse Temporal Gyri: The cortex is relatively thin, though varying slightly from place to place. Pyramidal cells are relatively sparse, particularly in Layers 2 and 3. Infragranular Layers 5 and 6 are relatively thick. The granular Layer 4 is well marked and contains numerous stellate or granular cells but is of only average thickness. Vertical orientation of cells is much less marked in the cortex in this area than in most other cortical areas, particularly in Layer 6.

9. Inferior Temporal Gyrus: The cortex here is of average thickness, with all layers well developed. The number of pyramidal cells in Layers 2 and 3 is rather low; there is a high concentration of stellate cells in Layer 4 and in superficial Layer 2. Layer 4 is of average thickness. There is a fair number of medium-sized pyramidal cells in Layer 5, but no large pyramidal cells. There is a moderate number of spindle cells in Layer 6.

10. Lateral Occipital Gyrus: The cortex here is relatively thin. The infragranular Layers 5 and 6 are particularly thin and cell-poor (variously oriented spindle, and medium and small pyramidal, cells). Pyramidal cells are scattered through Layers 2 and 3, and stellate cells are numerous in superficial Layer 2 and also Layer 4.

11. Calcarine Gyrus: The cortex is of average thickness and generally poor in pyramidal cells, only a few medium and large pyramidal cells being present. The granular Layer 4 is particularly thick, almost as thick as all the other layers in this section added together, and cell-rich (with stellate cells). There is a cell-free thin strip between Layers 4 and 5. There are also many stellate cells in Layer 2. Layers 2 and 3 contain rather widely scattered pyramidal cells, grading from small cells superficially to medium-sized cells deep. Layers 5 and 6 are thin and relatively cell-poor.

Pathologic Studies.—Because of the different types of nerve cells encountered in the cerebral cortex, different criteria were used in evaluating the changes within

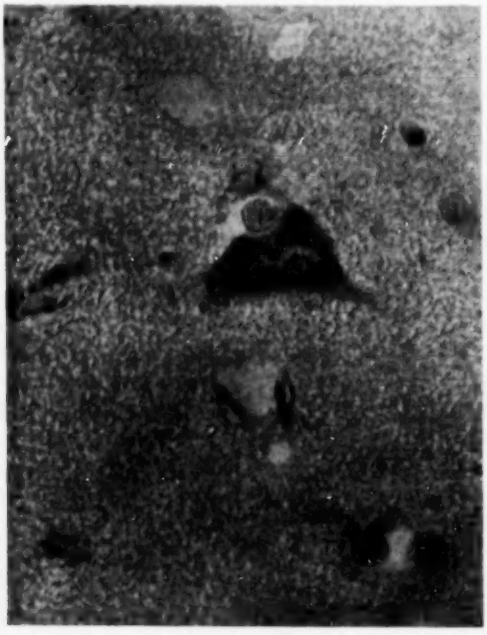

Fig. 1.—Section through the superior precentral gyrus in acute bulbar poliomyelitis, showing complete chromatolysis of a giant pyramidal cell.

the various cell elements. Since the same types of neurons, with the exception of the larger pyramidal cells, are present in all cortex sections, criteria used will be described by cell type.

1. Large and Giant Pyramidal Cells: This is the only cell type in which chromatolysis can be accurately judged, even when incomplete (Fig. 1). Swelling is also easily evaluated, owing to the sharp, angular contours of the normal cell. Fragmentation, pyknosis, chromatolysis (with ghost cell formation), eccentric nuclei, nuclear extrusion, satellitosis, and neuronophagia are all reliable guides to neuron damage for this cell type.

2. Medium and Small Pyramidal Cells: Complete chromatolysis can be distinguished in these cells, but partial chromatolysis is difficult to evaluate and was thus ignored for purposes of quantitating damage (Fig. 2). Satellitosis in the super-

ficial layers (to a maximum of three satellite cells) is so common normally that it was ignored. The other criteria which can be used fruitfully are fragmentation, pyknosis, neuronophagia, ghost cell formation, and nuclear extrusion (Fig. 3).

3. Stellate or Granular Cells: This is the most difficult cortical cell to evaluate. It is present in Layer 2, and especially in Layer 4. Useful criteria include only fragmentation and neuronophagia; other types of neuron pathology cannot be evaluated with any reliability. Since the cells are so densely and evenly packed in many of the areas (in Layer 4), reports of cell-free or cell-poor areas can also be accepted as reliable evidence of destruction of this type of neuron.

4. Spindle Cells: These cells are present mainly in the deepest cortical layer, Layer 6. They can be evaluated in much the same fashion as medium-sized pyramidal cells. Complete chromatolysis can be distinguished, as can severe degrees of

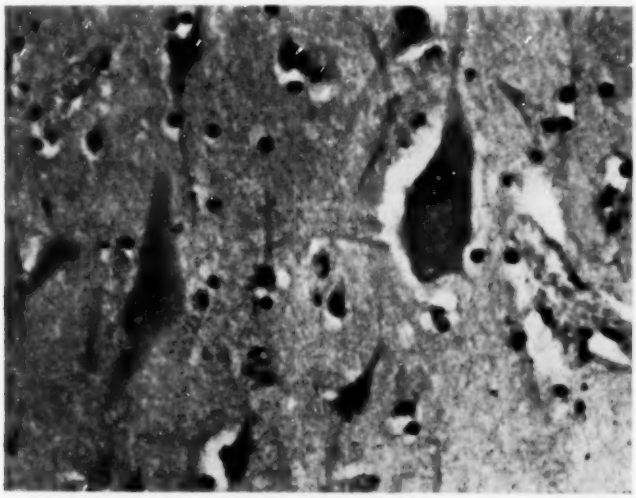

Fig. 2.—Section through Layer 3 of the superior temporal gyrus in a case of poliomyelitis with hypoxic symptoms. Note the complete chromatolysis within the medium-sized pyramidal cells. Some of the smaller cells are shrunken and pyknotic.

swelling (Fig. 4). Fragmentation, nuclear extrusion, neuronophagia, satellitosis, and ghost cell formation (a commonly seen type of pathology for this cell) can also be used. Pyknosis, if of severe degree, is of value.

5. Other Cell Types: Such cell types as Martinotti cells, horizontal cells, and stellate pyramidal cells are either not distinguishable in Nissl-stained sections from other cell types, or are of such sparse occurrence as to be of no importance in this type of study.

Neural Damage Differentiation.—Since many patients with bulbar poliomyelitis develop disturbances of respiration with prolonged periods of hypoxia, any unselected series would be expected to show brain changes due both to the infection and to hypoxia. To date, no attempt has been made to identify or to differentiate between these two types of neuronal changes. Since the cytological alterations can be very similar in these two conditions, it was felt that a careful survey of the case

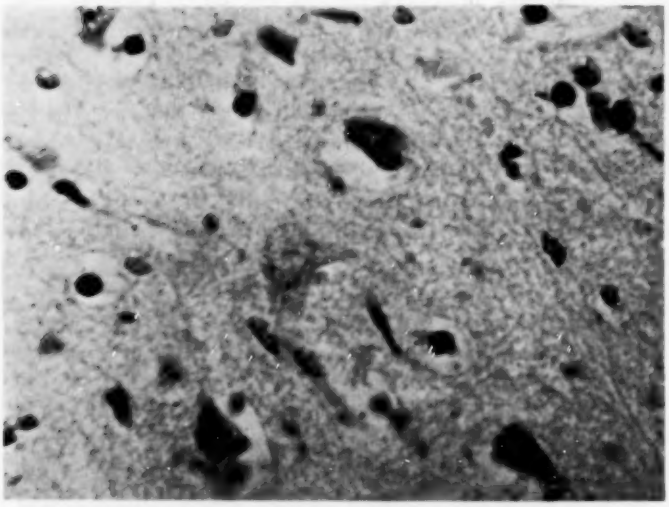

Fig. 3.—Section through the superior precentral gyrus in acute bulbar poliomyelitis. Note the ghost cell with almost complete destruction of the cell architecture.

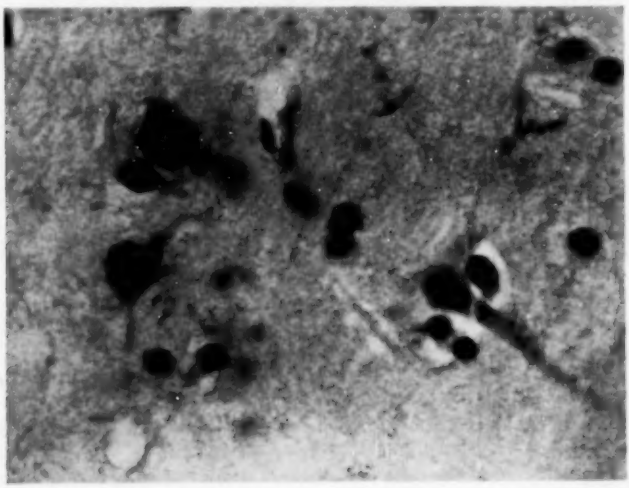

Fig. 4.—Spindle cells from Layer 6 of the precentral gyrus in a case of acute bulbar poliomyelitis. Note the complete chromatolysis of all the cells and the severe fragmentation and disappearance of some of the cell bodies.

histories would be the best method of determining which cases had suffered from hypoxia and probably had hypoxic changes within the brain. A study of the histories of our 75 cases showed 19 in which clinically the patients had long periods of hypoxia, lasting 2 to 10 days, prior to death. All these patients were restless, cyanotic, and even comatose. They all manifested severe bulbar and obstructive symptoms and were treated by respirator and/or tracheotomy. In these 19 cases we felt certain that any cortical alterations observed must be the result of both the disease itself and an associated hypoxia. The remaining 56 were cases of very acute

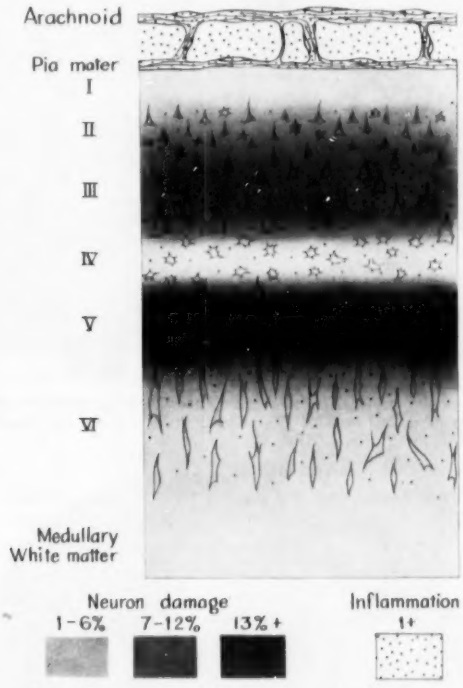

Fig. 5.—Laminar arrangement of the lesions in acute bulbar poliomyelitis as demonstrated by the comparative darkness of the shaded areas. Note the localization of the lesions to giant pyramidal cells of Layer 5 and the medium pyramidal cells of Layer 3.

deaths, with the entire illness lasting only a few days after the onset of bulbar symptoms. None gave any evidence of hypoxia. Because of the acuteness of the illness and the absence of evidence of hypoxia, it was felt that any changes observed in these cases probably were due to the disease alone. These latter cases were designated as our "acute cases," in contrast to the former group, which were called "subacute or hypoxic."

Histologic study of all 75 cases showed definite neuron pathology in 62 or 83%. All but 2 of these 62 cases had involvement of the medium and large pyramidal cells of the superior precentral region. The two cases lacking precentral damage both belonged to the subacute (hypoxic) group. Neuron damage in other areas of the cerebral cortex, either alone or in combination with the superior precentral

involvement, was as follows: inferior precentral area, 11; prefrontal area, 6; inferior frontal gyrus, 4; inferior parietal gyrus, 3; superior or transverse temporal gyrus, 2, and superior postcentral, superior parietal, inferior temporal, and lateral occipital regions, 1 each.

Acute Cases: Nerve cell damage was clear-cut and consistent and was strikingly localized to the pyramidal cells of the superior precentral gyrus, where 42,

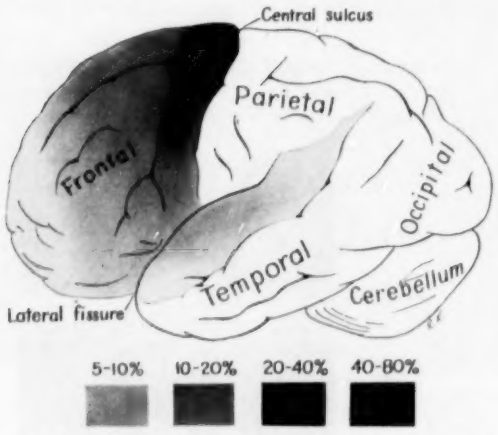

Fig. 6.—Severity of the cortical lesions in 56 cases of acute bulbar poliomyelitis, as demonstrated by the comparative darkness of the shaded areas. Note the localization of the lesions to the prefrontal and frontal areas.

TABLE 2.—*Brain Changes in Fifty-Six Cases of Acute Bulbar Poliomyelitis*

Area	Meningitis	Interstitial Cell Reaction	Neuronal Changes: Large Cells	Medium Cells	Small Cells	Total % of Alteration
Hippocampus	14	7	..	..	..	..
Gyrus cinguli	5	4	..	..	..	..
Inferior frontal	9	6	1	..	..	1.8%
Prefrontal	11	3	2	..	..	3.6%
Superior precentral	37	47	42 (12.4%)	40 (8.5%)	17 (0.5%)	75 %
Inferior prefrontal and postcentral	5	7	2	..	..	3.6%
Superior parietal	3	2	..	..	..	..
Inferior parietal	4	1	..	..	..	..
Superior and transverse temporal	3	1	..	..	..	..
Inferior temporal	2	..	..	..	..	..
Lateral occipital	1	..	..	..	..	..
Calcarine	1	..	..	..	..	..

or 75%, of the cases showed changes. The large and giant (Betz) pyramidal cells of Layer 5 were the most severely damaged, about 13% of these cells being involved. The medium pyramidal cells of Layer 3 were next most severely damaged, with about 8.5% of the cells showing changes. Only about 0.5% of the small pyramidal elements were injured. It would appear that in acute bulbar poliomyelitis the neuronal damage within the brain tends to be localized to the deeper Layers 3 and 5 of the superior precentral areas (Fig. 5). Very mild nerve cell changes were occa-

sionally observed within the inferior precentral or prefrontal gyri, while in a single case alterations were observed within the superior postcentral and inferior frontal gyri (Fig. 6 and Table 2).

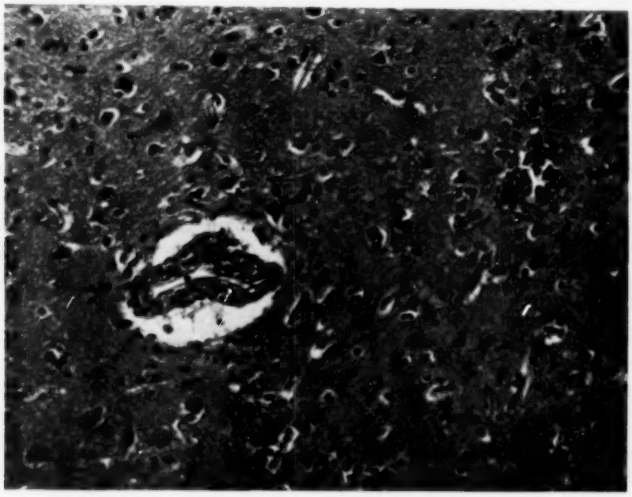

Fig. 7.—Focal area of inflammation within the precentral gyrus. The heavy layer of leucocytes is localized to the perivascular space, with mild involvement of the adjacent tissues.

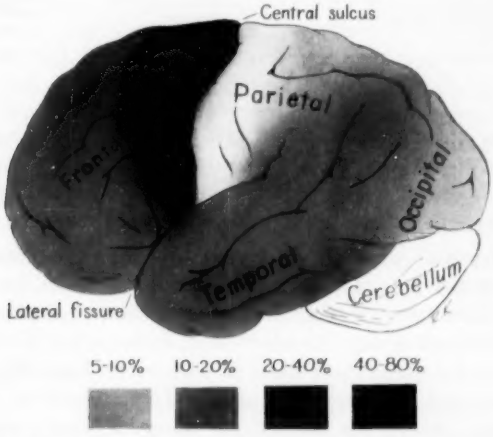

Fig. 8.—Severity of the cortical lesions in 19 subacute (hypoxic) cases of bulbar poliomyelitis, as demonstrated by the comparative darkness of the shaded areas. Note the diffuse nature of the involvement in contrast to the acute cases.

In all cases the commonest neuronal alteration consisted of a mild to moderate chromatolysis, usually perinuclear but occasionally diffuse (Figs. 1 and 2). Often the chromatolysis was accompanied by a definite swelling of the cell body. Many of the involved nerve cells were fragmented with a ruptured cell membrane. Ghost

cells were observed in about 40% of the sections containing damaged cells (Fig. 3). Pyknosis and neuronophagia were infrequent, while satellitosis and nuclear eccentricity and extrusion were extremely uncommon.

Relatively widespread and extensive inflammatory changes were also present in this group of acute cases. Meningeal inflammation was common and involved the entire surface of the brain, being much more frequent and extensive over the motor area. The interstitial cell changes within the cortex were also extensive and consisted of diffuse, as well as focal, areas of inflammatory elements. A large number of the smaller vessels were surrounded by cuffs of mononuclear cells (Fig. 7). Glial nodules were few in number. This mesodermal-glial reaction, in contrast to the meningitis, was much more restricted in its localization. The most intense involvement was observed in the superior precentral area, where 47 of the 56 cases showed changes. Most of these inflammatory changes were localized around the motor cortex, implicating primarily the frontal, prefrontal, and postcentral areas,

TABLE 3.—*Brain Changes in Nineteen Cases of Subacute (Hypoxic?) Fatal Bulbar Poliomyelitis*

Area	Meningitis	Interstitial	Neuron Change	Neuron Changes in Acute Cases
Hippocampus	5	4	6-32%	.....
Gyrus cinguli	..	..	.....	.....
Inferior frontal	2	4	3-16%	1- 1.8%
Prefrontal	5	3	7-37%	2- 3.6%
Superior precentral	6	14	15-79%	42-75 %
Inferior precentral and postcentral	3	6	7-37%	2- 3.6%
Superior parietal	3	1	1- 5%	.....
Inferior parietal	3	3	4-21%	.....
Superior and transverse temporal	..	2	3-16%	.....
Inferior temporal	2	..	4-21%	.....
Lateral occipital	..	..	1- 5%	.....
Calcarine	..	..	.....	.....

although to a less extent than the motor area (Table 2). The focal infiltrates were often accompanied by relatively diffuse neuronal changes, although in some cases the inflammatory reaction was not associated with any nerve cell changes. Neuronal damage was observed in the absence of inflammatory changes in only three cases.

Subacute (Hypoxic) Cases: The neuron damage in these cases was also most intense in the superior precentral area, where 15, or 79%, of the 19 cases showed involvement. In these cases the degree and the localization of the cell damage was very similar to the acute group. About 20% of the large and giant pyramidal cells of Layer 5 appeared damaged, and about 15% of the medium cells of Layer 3 were involved. Layers 1 and 4 were entirely spared. However, in contrast to the acute cases, the neuronal damage was much more widespread and involved more extensive areas of cortex (Fig. 8 and Table 3). Practically all cortical areas showed changes in at least some of the cases, although the cell damage was generally mild and diffuse and did not show any tendency to implicate only the deeper layers. If one can assume from a study of the acute cases (Table 2) that poliomyelitis primarily involves the deeper layers of the precentral gyrus, then one can surmise that the widespread implication of other cortical areas in the subacute group was probably the result of hypoxia rather than of the disease process itself.

The nature of the neuronal changes in the two groups did not differ enough to offer any differentiating features. Perinuclear chromatolysis, cell swelling, and some fragmentation were the commonest changes observed and were identical to those observed in the acute cases.

Meningeal involvement and mesodermal-glial changes were common in most of the subacute cases and showed little difference in extent and intensity from similar alterations observed in the acute cases.

COMMENT

It is apparent from our studies that poliomyelitis does consistently involve the cerebral hemispheres, producing meningitis, mesodermal-glial reaction, and neuron damage, the two former changes being fairly mild and diffuse, while the latter is strictly localized to the precentral gyrus and even has a layer specificity. One can therefore speak correctly of a polioencephalitis. It is somewhat surprising, in view of the frequent histologic involvement of the brain, that clinical symptoms referable to the brain are not more frequent and more striking. This lack of clinical evidence of involvement of the motor cortex is probably due to the fact that in none of our cases were more than 15 to 20% of the large motor cells damaged, and in many of these the pathologic process was reversible. Certainly none of our cases showed enough involvement to produce a spastic hemiplegia or paraplegia, such as has been suggested by the studies of Strümpell.[1]

The rather diffuse and often intense involvement of the meninges, particularly over the precentral area, might suggest a meningeal spread of the disease into the underlying cortex. Certainly some involvement of the cortex probably does result from the meningitis, since the inflammatory process can be followed from the surface along the perivascular spaces of the cortical vessels. However, in many of our cases deep cortical foci of inflammation and neuron damage did occur within the precentral area entirely independent of any meningeal involvement. In such cases one must seek some other method or route of infection. Fairbrother and Hurst [41] have suggested that the virus spreads along the nerve fibers. In their intracerebrally inoculated monkeys, the lesions first appeared homolaterally in the thalamus, hypothalamus, midbrain, pons, and medulla and then spread contralaterally to the thalamus and motor cortex. They felt that the only explanation for these bilateral, symmetrical precentral lesions was that this area of the cortex is most intimately connected by the great afferent and efferent tracts to the midbrain and brain stem and that the cortical infections take place from the lower centers, where the lesions are marked and the virus content high. Sabin and Ward [42] studied the distribution of the virus in fatal cases and found the virus with ease in the cord, medulla, midbrain, thalamus, and motor cortex, but not in the frontal and occipital cortex. These studies substantiate the findings of Fairbrother and Hurst and again suggest a neural spread of this disease to the brain.

In order to study this problem further, it was felt that a preliminary survey of the pathologic lesions throughout the entire nervous system in a series of our cases might offer some evidence as to the mode of involvement and the route of spread of the disease. Ten unselected cases were studied, and the nature and intensity of the histologic changes were recorded in all regions of the nervous system, on the basis of 1+, for the mildest involvement, to 8+ for the severer changes (Fig. 9).

If on the basis of such a rating the 10 cases are averaged, the degree of involvement in the various areas of the nervous system can be tabulated, as in Table 4. It is readily apparent that the relative intensity and nature of the involvement throughout the nervous system are constant with the exception of the basal nuclei, which were spared. This uniform intensity of tissue damage would at least suggest a blood stream dissemination of this disease.

It is surprising that the role of hypoxia in the production of cerebral lesions in poliomyelitis has not received more attention. It is apparent that a study of the neuronal alterations themselves would be of no help, since the nerve cell changes

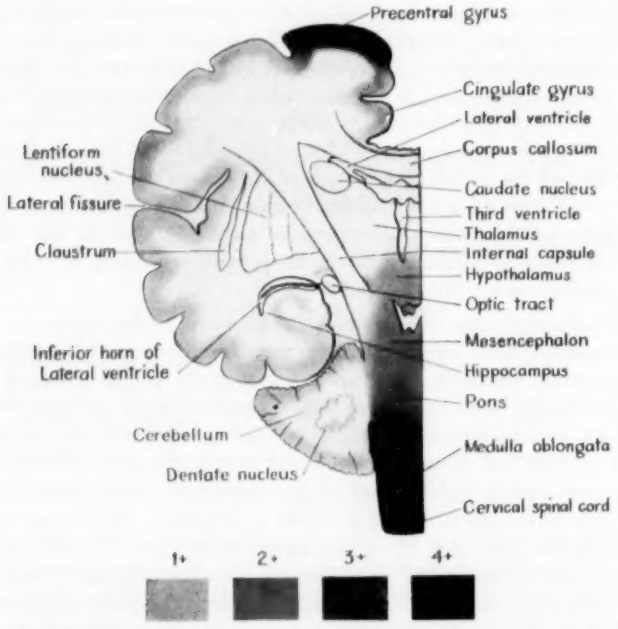

Fig. 9.—Distribution and severity of the lesions throughout the central nervous system in 10 cases of poliomyelitis, as demonstrated by the comparative darkness of the shaded areas.

are fairly similar in all acute processes, be it toxic, infectious, or hypoxic. Since it seems fairly certain that poliomyelitis will usually implicate only the pyramidal elements of the motor cortex, other cell changes must be related to the associated hypoxia.

Descriptions of the location and types of lesions attributed to anoxia have varied, but the predominant changes usually have implicated the neuronal elements diffusely throughout the cerebral cortex and corpus striatum, with no tendency to select the motor areas. Hicks [43] felt that the pattern of involvement varied according to the etiology of the hypoxic agent, but in all agents there appeared to be a consistent diffuse implication of the cerebral cortex. In asphyxiated cats, Orthmayr [44] found diffuse neuronal changes within the cerebral and cerebellar cortex, as well as in the cornu ammonis and the basal nuclei. Morrison [45] in anoxic monkeys observed nerve

cell damage within the cerebral cortex, globus pallidus, and thalamus. The severest cortical lesions occurred within the frontal and temporal lobes. In two cases of anoxia from high altitudes Titrud and Haymaker [46] reported diffuse changes throughout the cerebral and cerebellar cortex.

The nature of the neuronal changes in hypoxia has shown considerable variation and has ranged from enlarged perineural spaces with shrinkage of nerve cells (Courville [47]) to chromatolysis, vacuolation, pyknosis, and chronic shrinkage (Burdick and associates [48]). There is considerable disagreement as to the presence of specific laminar arrangement of the cellular degeneration in anoxia. Thorner and Lewy,[49] Morrison,[45] and Gildea and Cobb [50] reported such degeneration in experimental animals, and Löwenberg [51] and Titrud and Haymaker [46] observed similar changes in man. However, most investigators have emphasized the tendency for the lesions to implicate the cerebral gray matter, without any tendency to select any particular cortical region (Alpers [52]; Courville [47]; Wilson and Winkleman [53]; Döring [54]).

TABLE 4.—*Average Degree of Involvement of the Entire Nervous System in Ten Unselected Cases of Poliomyelitis*

Level	Inflammatory	Nerve Cell Damage
Spinal cord	3.6+	4 +
Medulla	4.6+	5 +
Pons	4.2+	4.7+
Midbrain	3.9+	3.8+
Hypothalamus	4.3+	4.1+
Thalamus	0	0
Basal ganglia and insula	0	0
Cerebrum	3.2+	2.4+
Cerebellum	2.6+	2.9+

A comparison of the changes within the brain reported as generally occurring in anoxia, regardless of the cause, with the changes in our cases of subacute poliomyelitis readily shows a marked similarity in the histopathologic findings as regards both distribution and laminar arrangement of the lesions. However, since our cases also had an associated poliomyelitis, one would expect to find an increased frequency of lesions around the motor area as a result of the basic disease process.

SUMMARY AND CONCLUSIONS

The cerebral hemispheres in 75 cases of bulbar poliomyelitis were studied. Of these cases, 56 were acute and clinically showed no respiratory difficulties, while 19 were subacute and clinically had marked hypoxia prior to death.

Meningeal involvement was extremely common and was observed in 85% of our cases, all cortical areas being implicated in at least some of the cases. This meningeal involvement was invariably mild and bore little correlation to the inflammatory or neuronal changes within the underlying brain tissue.

In the 56 acute cases, extensive nerve cell damage was observed in 42, or 75%. These neuronal changes were strikingly localized to the large and giant pyramidal cells of Layer 5 and the medium pyramidal cells of Layer 3 of the motor cortex.

The 19 subacute (hypoxic) cases showed neuronal damage in 15, or 79%. The nerve cell damage was more widespread, implicating almost all cortical areas in at least some of the cases. It was felt that the neuronal damage in cortical areas outside the motor cortex in these cases was probably due to hypoxia rather than the disease itself.

A survey of the pathologic changes throughout the nervous system in 10 unselected cases revealed a most consistent and uniform involvement in all areas exclusive of the basal ganglia, suggesting some uniform method of spread of the infection, such as the vascular system.

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POLIOMYELITIS

X. The Cerebellum

A. B. BAKER, M.D.
AND
SAM CORNWELL, Ph.D.
MINNEAPOLIS

THROUGHOUT the literature there are numerous references to the involvement of the cerebellum in poliomyelitis; still clinical evidence of disturbances of this region of the nervous system is generally lacking. This may be due to the fact that it is somewhat difficult and unsatisfactory to examine cerebellar function in patients severely paralyzed with spinal poliomyelitis or critically ill with bulbar or respiratory poliomyelitis. Certainly, in most studies evidence of residual cerebellar disturbances in patients that have recovered from this illness is generally lacking. Because of the volume of our material it was felt that a detailed study of the cerebellum might be of value in indicating the actual nature and extent of the cerebellar lesions in this disease.

As early as 1898 Médin [1] reported cases of poliomyelitis in which the chief finding was incoordination. He referred to these cases as the ataxic, or cerebellar, form of the disease. He described these patients as having an uncertain, staggering, and wide-based gait, similar to patients with Friedreich's ataxia. Wickman [2] also reported cases in which ataxic symptoms were conspicuous and were associated in many cases with diminution or loss of tendon reflexes. Occasionally the cerebellar disturbances were mild and often hidden by the other, more classical findings of the disease. In a pathologic study of four cases, Wickman observed fairly intense changes in the cerebellum in three. These consisted of perivascular infiltrations involving both the cortex and the white matter primarily of the vermis. The meninges surrounding the cerebellum also showed mild scattered areas of mononuclears.

Ataxia has frequently been mentioned in subsequent epidemics by Zappert,[3] Lindner and Mally,[4] Lemmon,[5] Horányi-Hechst,[6] and Fanconi and associates.[7] Horányi-Hechst, in a study of 38 fatal cases, observed cerebellar changes in 22, or 58%. Fanconi and his associates described cerebellar changes in only 3.2% of their 375 cases. Lemmon reviewed in detail the clinical symptoms and signs in 49 patients with acute poliomyelitis and found only one case that clinically represented cerebellar poliomyelitis. The symptoms in this case consisted of extreme lateral nystagmus, vertigo, intention tremor, and ataxia.

There is a great diversity of opinion in the literature regarding the distribution of the lesions within the cerebellum in poliomyelitis. Generally most investigators feel that the Purkinje cells are spared and that most of the lesions are limited to the

From the Division of Neurology, University of Minnesota Medical School.

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vermis and the roof nuclei (Chown,[8] Horányi-Hechst,[6] Swan,[9] Howe and Bodian [10]). Horányi-Hechst, in a very comprehensive study of 38 cases, found the cerebellum involved in 22 cases implicating primarily the cerebellar nuclei, chiefly the tectal and dentate. There were some inflammatory changes within the molecular layer but no involvement of the Purkinje layer. Almost identical distribution of lesions were reported by Swan in two cases of poliomyelitis. Howe and Bodian, in a report of 13 fatal cases, observed only a mild involvement of the cerebellar cortex with many lesions within the vestibular and roof nuclei. This localization to the roof nuclei was substantiated by Hurst [11] in the experimental disease in monkeys. The cerebellar lesions were limited to the dentate nucleus, the roof nuclei, and the white matter.

In contrast to the above observations, both Környey [12] and Richter [13] reported definite alterations within the Purkinje cells. Környey in eight cases observed the pia mater to be filled with leucocytes, which had extended into the cerebellar cortex to involve both the molecular and the Purkinje layers. Richter studied in detail a fatal case in a 14-year-old boy. The cerebellar changes were insignificant but consisted of retrogressive changes of the cells of both the dentate nucleus and the Purkinje layer, with loss of a number of Purkinje cells.

A few investigators have emphasized the white matter lesions within the cerebellum in this disease. Fischer and Stillerman,[14] in one case, observed inflammatory lesions only within the white matter of the cerebellum. Abramson,[15] in a study of 43 cases, found cerebellar lesions in 5 localized below the cellular layers, chiefly among the fibers radiating out from the cortex.

PRESENT STUDY

The cerebellum was available for study in 75 fatal cases of bulbar poliomyelitis. Sections were taken from many areas including the meninges, the molecular layer, the Purkinje layer, the granular layer, the white matter, the dentate nuclei, and the roof nuclei. Sections from all areas were prepared with the Nissl stain, hematoxylin and eosin, and Weil's stain. Since each of the various regions of the cerebellum studied has a different structure, it might be well briefly to review the normal architecture and the criteria adopted by us as evidence of tissue damage.

1. *Molecular Layer.*—This layer contains only scattered neurons consisting of small superficial stellate cells near the surface and a few small stellate cells, known as basket cells, in its deeper layers and between the Purkinje cells. These stellate cells contain a small round nucleus and a small amount of cytoplasm arranged in a stellate form and containing small amounts of diffuse, finely granular Nissl substance. These stellate cells are rarely implicated in poliomyelitis; hence no criteria for their damage was established.

2. *Purkinje Layer.*—The structure of these cells is well known. They are large uniform pear- or flask-shaped cells arranged in a relatively thin layer one to two cells in thickness (Fig. 1*A*). The nucleus is large, round, vesicular, and centrally placed and contains a conspicuous nucleolus. The cell body contains abundant Nissl granules, which are irregular in shape and moderately large.

Four types of changes were accepted as evidence of Purkinje cell damage, namely, chromatolysis, fragmentation, ghost cell formation, and pyknosis (Fig. 1*B*). The chromatolysis had to be fairly extensive or specifically limited to the peripheral or perinuclear area of the cell. Occasionally the chromatolysis was accompanied by cell swelling, although this latter change was a little difficult to evaluate in cells as large

as the Purkinje cells. Fragmentation was limited to the cell body, often with extrusion of part or all of the cytoplasm. Pyknotic changes consisted of shrinkage and marked deformity of the cell body as well as the nucleus.

Coiled apical dendrites and a diffuse loss of the definition of the Nissl granules were too unreliable to be considered safe evidence of cell damage. Even defects in the arrangement and layers of Purkinje cells were not considered significant unless one-quarter or more of the folium was free of Purkinje cells.

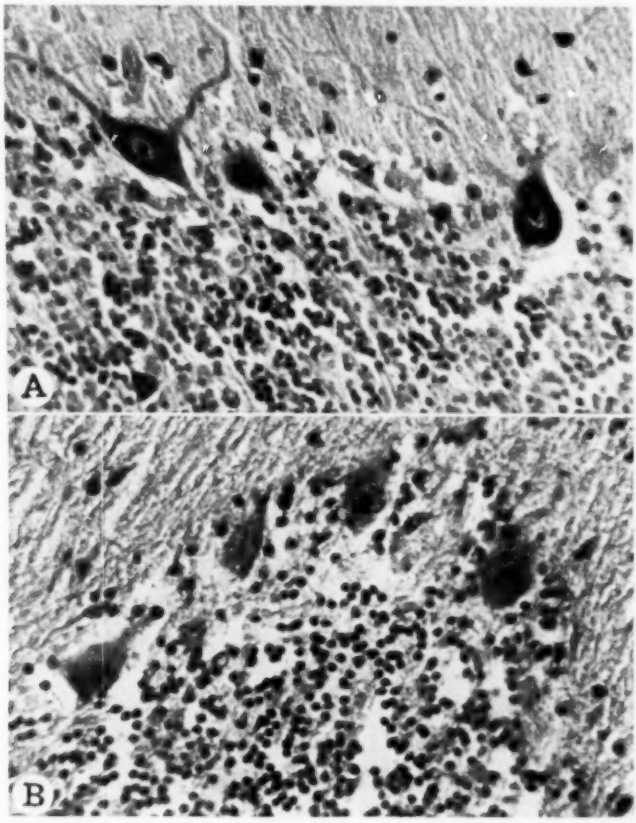

Fig. 1.—*A*, normal cells of the Purkinje layer. These cells are large pear-shaped elements with a distinct nucleus and nucleolus. *B*, Purkinje cell changes in acute bulbar poliomyelitis. There is complete chromatolysis and some fragmentation of the cells.

3. *Granular Layer.*—This layer is composed of many closely packed, small granule cells interspersed with occasional larger Golgi Type II cells. The granule cells are among the smallest neurons in the nervous system and contain a moderate-sized round nucleus and little or no visible cytoplasm or Nissl material. The Golgi cells have larger, more vesicular nuclei and definite, angular cell bodies with a moderate amount of indefinitely granular Nissl material (Fig. 1*A*).

Damage to the granule cells is difficult to detect. Severe fragmentation or distortion of the nuclei was the only detectable pathologic change noted in these cells. Complete destruction of these elements with areas of devastation within this layer would be obvious but was not seen in any of our cases. There was no evidence of damage to the Golgi Type II cells in the granular layer.

4. *Dentate Nucleus.*—This structure is composed of globular or fusiform cells ranging in size from 22 to 35 μ in diameter (Fig. 2*A*). The cells are arranged in a

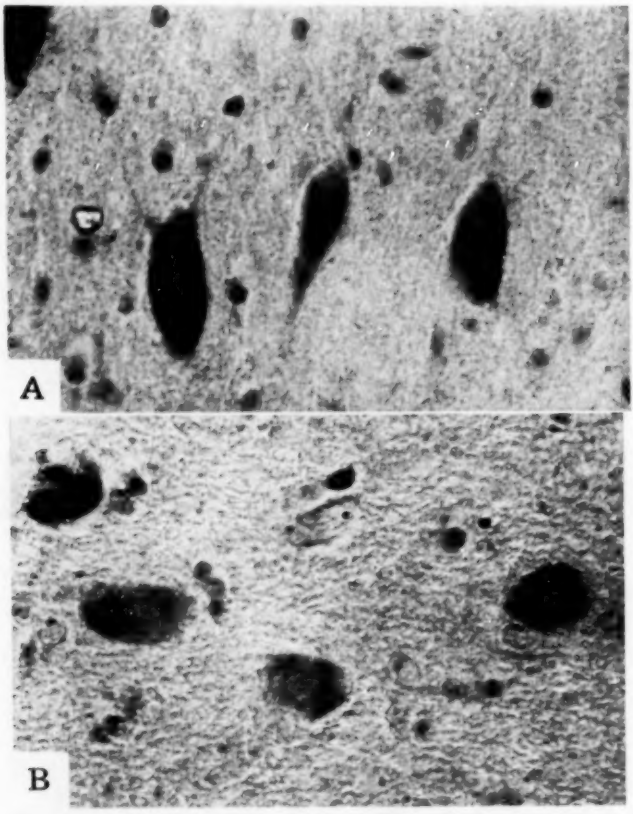

Fig. 2.—*A*, normal cells of the dentate nucleus. These cells are 22-35 μ in diameter and contain a very finely granular Nissl material. *B*, section through the dentate nucleus in a patient who died of acute bulbar poliomyelitis. The cells have lost their staining properties and show beginning fragmentation.

rather irregular alignment of four to six rows. These cells have a central round nucleus and an abundant cytoplasm containing small granular Nissl bodies. Pigment inclusions or vacuoles are often present in the cell cytoplasm, giving the appearance of partial chromatolysis. Because of this latter finding, only complete chromatolysis can be interpreted as evidence of cell damage (Fig. 2*B*). Fragmentation of the cell body, ghost cell formation, neuronophagia, and pyknosis were additional reliable evidence of cell damage.

5. *Roof Nuclei (Emboliform, Globose, Fastigial).*—Cells of the emboliform nucleus are similar in structure to those of the dentate nucleus but are smaller in size. Cells of the globose nucleus resemble those of the emboliform nucleus. The fastigial nucleus contains both large and small cells. They are variable in form as well as size, and may be stellate, triangular, or fusiform in shape (Fig. 3). The Nissl granules and the finer nuclear and cytoplasmic structure of the roof nuclei are similar to the cells of the dentate nucleus. The criteria for cell damage in the roof nuclei are the same as for the dentate nucleus, although such changes were less commonly observed.

PATHOLOGIC STUDIES

Involvement of the cerebellum in poliomyelitis is relatively mild, but some degree of pathology is seen in a majority of cases. Of the 75 cases studied, 77% showed at least a minimal amount of inflammatory and/or neuronal change in some areas of the cerebellum. The types of inflammatory or nerve cell changes were very similar

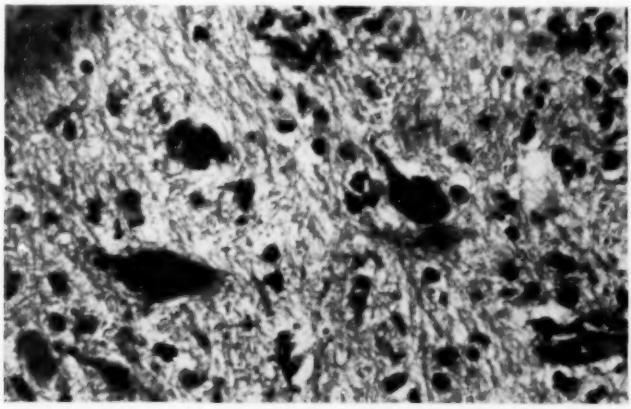

Fig. 3.—Normal fastigial nucleus. Note the fusiform shape of these cells and the well-defined Nissl granules.

to those observed in other areas of the nervous system. The commonest site of tissue damage occurred in the dentate nucleus and in the cerebellar cortex in the region of the vermis (Table).

Meninges.—Inflammatory changes within the meninges were observed in 40% of the cases and were most frequently encountered over the vermis (39%), the anterior lobe (23%), and the cerebellar hemispheres (17%) (Fig. 4*A* and *B*). In 24% of the cases the meningeal changes were the only alterations observed, no detectable changes being present within the cerebellar substance.

The meningitis was usually mild and consisted of a relatively diffuse infiltration of round cells with a few polymorphonuclears within the leptomeninges and subarachnoid space. In only an occasional, very acute case did the polymorphonuclears predominate. Occasionally a large number of macrophages were present. The meningeal vessels were frequently surrounded by irregular layers of mononuclears, and in some cases the inflammatory elements extended to the vessels of the underlying cerebellar tissues or into the sulci between the folia.

Molecular Layer.—Except for the dentate nucleus, the molecular layer was the commonest site of inflammatory pathology within the cerebellar substance (Table). This layer was involved in the region of the vermis in 29% of the cases (Fig. 5) and in the region of the cerebellar hemispheres in 10%. In 5% of the cases the inflammatory changes were extensive enough to extend inward to implicate the granular layer of the cerebellum.

This mesodermal-glial reaction usually appeared as a mild to a moderate focal inflammation, often with perivascular cuffing and occasionally showing a diffuse spread into the adjacent tissues. The inflammatory foci were composed of a mixture of mononuclears as well as polymorphonuclears, usually with the former predomi-

Summary of Cerebellar Pathology in Seventy-Five Cases of Fatal Bulbar Poliomyelitis

Region	Pathology	
	Inflammation, % of Cases	Neuron Damage, % of Cases (Average % of Cells Damaged)
I. Meninges		
A. Over anterior lobe	23 (8% alone)	.....
B. Over vermis	29 (23% alone)	.....
C. Over hemisphere	17 (13% alone)	.....
II. Molecular layer		
A. Of vermis	29	0
B. Of hemisphere	11	0
III. Purkinje cell layer		
A. Of vermis	25	25 (8%)
B. Of hemispheres	10	11 (5.5%)
IV. Granular layer		
A. Of vermis	4	± in 2%
B. Of hemisphere	1+	0
V. Subcortical white matter		
A. Of vermis	5	.....
B. Of hemisphere	3	.....
VI. Roof nuclei		
A. Dentate nucleus	57	28 (7%)
B. Emboliform nucleus	19	8 (5%)
C. Globose nucleus	16	7 (5%)
D. Fastigial nucleus	15	3 (5%)

nating. Occasionally, small areas of demyelination developed around or adjacent to these inflammatory areas.

Purkinje Cell Layer.—The inflammatory foci within the molecular layer often extended into or even through the Purkinje layer of cells, but foci limited to this layer were not encountered.

Within the vermis 25% of the cases showed damage to the Purkinje cells. The neuronal damage was never extensive, implicating only about 8% of the cells. In 22% of the cases the cell changes occurred in the same areas as the inflammatory foci, while in a number of cases the Purkinje cell alterations were accompanied only by a meningitis of the overlying area. In 12% of the 75 cases the Purkinje cells within the hemispheres were implicated, about 5 to 6% of the cells being damaged (Table). In about half of these cases there was no associated inflammatory pathology.

The most frequent cell change was chromatolysis, oftenest perinuclear, with complete dissolution of all Nissl substance except for a thin band or crescent around

the cell margin (Fig. 1*B*). Swelling of the Purkinje cells often accompanied the chromatolysis. The next most frequent cell change was fragmentation of the cell body associated with eccentricity, fragmentation, and distortion of the nucleus. Complete destruction of the cell contents with loss of staining properties occasionally resulted in ghost cell formation. Pyknosis of both cell body and nucleus did occur but was uncommon.

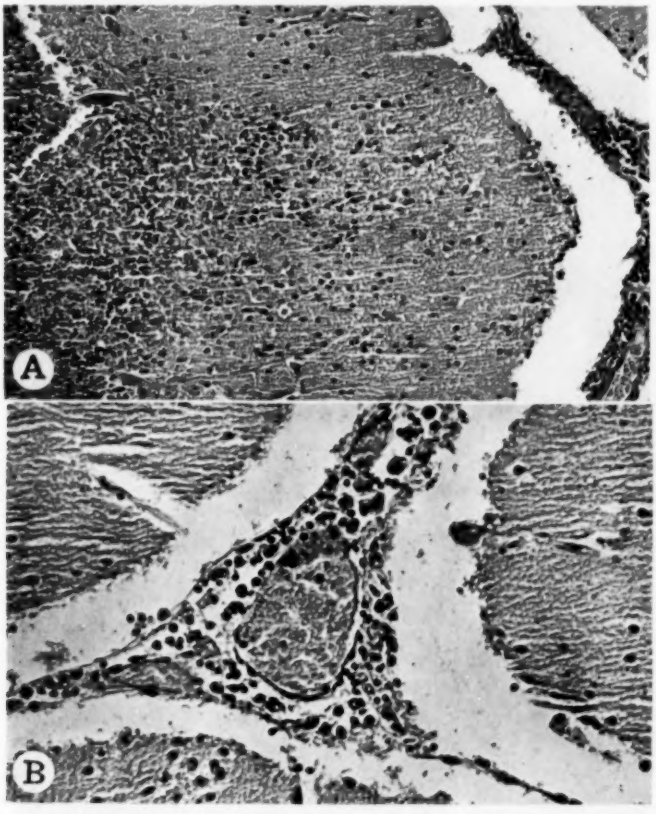

Fig. 4.—*A*, section through the molecular layer over the cerebellar vermis. There is a thin layer of inflammatory elements covering this surface of the cerebellum. *B*, a layer of perivascular leucocytes surrounding a vessel within the folia of the cerebellum.

Granular Layer.—In the occasional case the inflammatory process appeared to extend from the molecular layer into the granular layer, producing focal areas of round cell infiltration. Such changes were seen in the vermis in 4% of the cases and in the hemispheres in 1% (Table).

Unequivocal evidence of neuronal damage was not observed in any of the cases studied. Minimal changes of questionable significance were sometimes seen, consisting of a few small, relatively "cell-poor" areas and very small numbers of fragmental cells.

Medullary White Matter.—Foci of inflammation, often accompanied by perivascular cuffing and petechiae, were observed within the region of the dentate and roof nuclei (Fig. 6). About 5% of the cases showed "peridentate" inflammatory foci, while 3% had similar foci within the white matter of the cerebellar hemispheres.

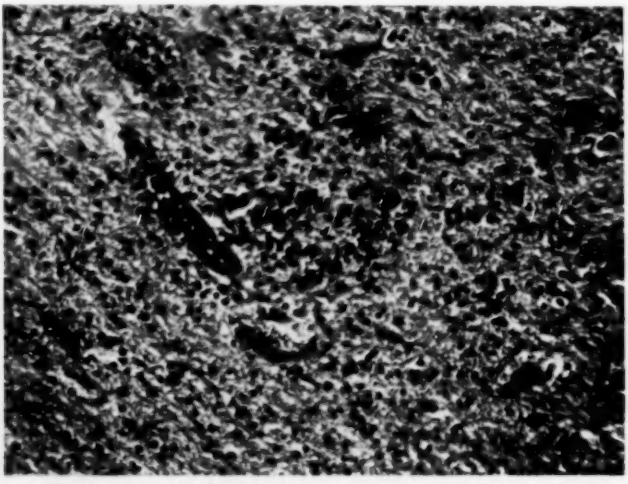

Fig. 5.—Molecular layer of the cerebellum from a case of acute bulbar poliomyelitis. There is a focal area of inflammatory cells with some spread of the inflammation to the adjacent tissue.

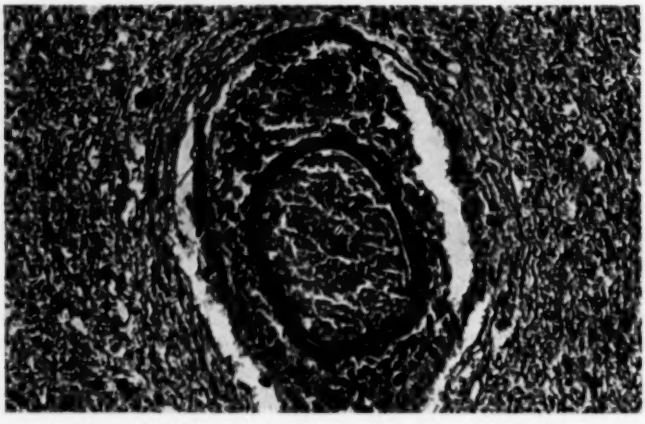

Fig. 6.—Section through the white matter in the region of the dentate nucleus. There is a heavy layer of leucocytes within the perivascular space.

Dentate Nucleus.—The dentate nucleus and the subjacent white matter were the commonest sites of inflammatory involvement within the cerebellum (Table). Fifty-seven per cent of all cases contained inflammatory changes within the dentate nucleus, and in 5% of these cases the inflammatory process had extended into the

peridentate white matter. There were small to medium-sized foci of both round cells and polymorphonuclears, often associated with perivascular cuffing and occasionally accompanied by small areas of demyelination.

Significant neuronal damage was noted in 28% of the cases. The commonest cell change was fragmentation of the cells, often with complete disruption of the cell. Less commonly, ghost cell formation and pyknosis were observed. Chromatolysis was difficult to evaluate because of the irregular distribution and size of the Nissl granules and the frequent presence of pigment and vacuoles displacing the Nissl substance. However, in a few cases complete chromatolysis was seen, which, no doubt, was of pathologic significance (Fig. *2B*).

Roof Nuclei.—Inflammatory foci in the region of these cerebellar nuclei situated in the roof of the fourth ventricle were observed in 19% of all the cases. Neuronal damage was much less frequent, being observed in 3 to 8%. The fastigial nucleus was seldom involved. Only 3% of the cases showed changes within this nucleus. The globose nucleus was implicated in 7% and the emboliform nucleus in 8%, of the cases. The degree of cell damage was similar in all these nuclear groups, about 5% of the cells being involved (Table). The neuronal changes were similar to those seen in the dentate nucleus and consisted chiefly of fragmentation accompanied by some pyknosis, ghost cell formation, and, rarely, complete chromatolysis.

COMMENT

It is apparent from a study of our cases that the cerebellum is frequently implicated in poliomyelitis, even though clinical manifestations of such involvement is rarely seen. No doubt the chief reason for the infrequent cerebellar symptomatology is the mildness of the tissue changes within the cerebellum. In none of our cases was there ever more than 8% of the cells damaged, and in most nuclear groups the cell damage was less than this (Table). The frequency of the meningeal reaction and the inflammatory foci leave no doubt that the virus does implicate the cerebellum. It is possible that some of the neuronal changes might be due to the associated hypoxia that so often accompanies severe cases of fatal bulbar poliomyelitis. To check this factor, the case histories of all 75 cases studied were reviewed to determine which presented clear-cut evidence of hypoxia. Of our 75 cases, 57 presented a very acute history with rapid death and no evidence of hypoxia. In the remaining 18, the illness was prolonged with definite evidence of hypoxia consisting of long periods of dyspnea, cyanosis, and the need for respiratory aids, including tracheotomy. Comparison of these two groups of cases showed that the most striking differences consisted of a somewhat greater incidence of neuronal damage within the Purkinje layer, which was implicated in 22% of the acute cases and 39% of the chronic cases. In the dentate nucleus, the acute cases showed more frequent neuronal changes than did the chronic. From these observations one feels justified in concluding that the cerebellum, in contrast to the cerebral hemispheres, is not too readily affected by hypoxia and that in bulbar poliomyelitis the cerebellar alterations are chiefly due to the disease itself.

The distribution of the lesions within the cerebellum emphasizes a most striking feature of this disease, namely, its tendency to implicate nerve cells. Practically all cell groups within the cerebellum were involved to some degree, with the severest damage to the dentate nucleus and the Purkinje layer (Fig. 7). It has been sug-

gested that the poliomyelitis virus tends to limit itself to motor cells except in the severest cases. Certainly the widespread alterations within all nuclear groups of the cerebellum, as well as the striking damage to the reticular and tegmental cells, speak against such specificity.

The cerebellar findings must also be given consideration in formulating any concepts concerning the spread of this disease within the nervous system. It has been suggested by Fairbrother and Hurst [16] that the virus spreads along the nerve fibers and, therefore, this disease tends to show predilection for certain systems, such as the motor system. However, the widespread lesions within the cerebellum would certainly point to a more diffuse dissemination of the disease process and would emphasize the part played by the vascular system in the spread of this illness.

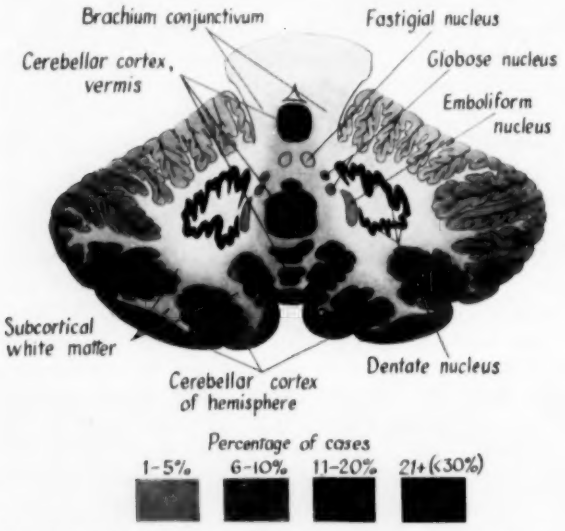

Fig. 7.—Intensity of tissue changes within the various regions of the cerebellum, as demonstrated by the comparative darkness of the shaded areas. Note the implication of all nuclear groups with a relative sparing of the white matter. The dentate nucleus and the cerebellar cortex are the most severely involved.

SUMMARY AND CONCLUSIONS

The cerebellum was studied in 75 cases of bulbar poliomyelitis.

It is apparent that the cerebellum is frequently implicated in poliomyelitis, even though clinical manifestations of such involvement are uncommon.

Of the 75 cases studied, 77% showed at least a minimal amount of inflammatory and/or neuronal change in some areas of the cerebellum.

Inflammatory changes within the meninges were observed in 40% of the cases and were most frequently encountered over the vermis.

Neuronal changes occurred within all nuclear groups of the cerebellum but were most frequent and severest within the dentate nucleus and the Purkinje layer of the vermis.

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PSYCHOMOTOR ATTACKS (PRIMARY AUTOMATISMS) OF SUBCORTICAL ORIGIN

B. FUSTER, M.D.
C. CASTELLS, M.D.
AND
B. RODRIGUEZ, M.D.
MONTEVIDEO, URUGUAY

THE INTERICTAL electroencephalographic study of patients with psychomotor attacks led one of us (B. F.), with Gibbs and Gibbs, to admit in 1947 * that this type of epileptic manifestations was accompanied by an anterior temporal epileptogenic focus, either unilateral or bilateral. This statement was confirmed by numerous subsequent investigations.

Nevertheless, more recent observations have led us to change our opinion and to admit the possibility of clinically primary automatisms (or psychomotor attacks) being likewise produced by discharges originating outside the temporal lobe, even when clinically they may not fall within the category of postictal automatisms.

In 1952 one of us (B. F.) with Schroeder and others [7] showed that an epileptogenic discharge originating in silent areas of the frontal cortex might produce typical psychomotor attacks.

Further, in some cases studied the subcortical origin of the psychomotor attacks had been suspected. Peculiar features of the interictal EEG suggested the possibility that an epileptogenic discharge originating in subcortical structures intimately related to the temporal lobe might give rise to a typical ictal automatism.[1] Nevertheless, definite proof was lacking.

In this paper we propose to show that an epileptogenic discharge originating in the diencephalic structures responsible for the clinical and electroencephalographic aspects of petit mal epilepsy may likewise produce ictal automatism identical to those produced by discharges originating in the silent areas of the temporal lobe.

MATERIAL AND METHOD

Material.—CASE 1.—O. R. Age 23. Major and minor crises: major crises of grand mal type, beginning at age of 16 years and repeated once a month, both while awake and during sleep. Minor crises: sometimes absences and on other occasions ictal automatisms (not preceded by any of the known cortical epileptic phenomena). Two instances of sleepwalking during infancy. No personal or family history of interest. Neurological and laboratory findings normal.

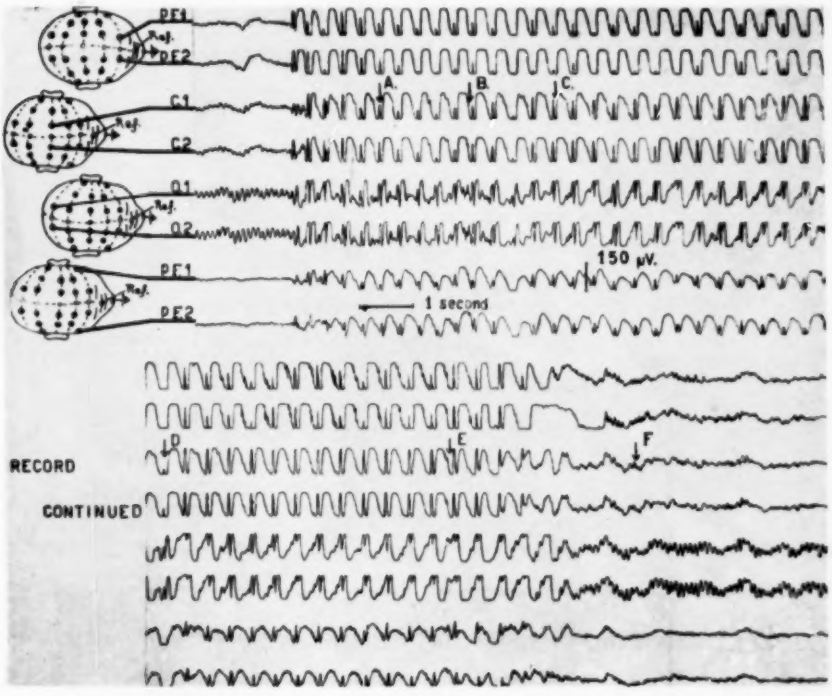
Read at the Postgraduate Course of the Neurological Institute, Faculty of Medicine, Montevideo, Uruguay, Dec. 19, 1951.

* References 3 through 5.

CASE 2.—O. C. Age 18. No major, but only minor attacks: absences and automatisms of brief duration, but complex (staring and inquiring gaze, with procursive, searching, gustatory, and chewing movements), which began at the age of 16. The absences were repeated every five minutes.

Comment.—As shown later, the minor forms of crises were in both cases of varying degrees, ranging from mere absences to elaborated and prolonged automatisms, habitually observed in temporal epilepsy.

EEG Studies.—In both cases the patients sought consultation because of the automatisms, in spite of their having absences, and one of them crises of grand mal. The automatisms were frequently complex and always of primary type, for which reason the cases were diagnosed as



Ictal EEG of a brief automatism of 18 seconds' duration from Case 2.

Bipolar push-pull recording, with common reference electrode on nose tip. Position of electrodes on head shown according to Jasper's system of coordinates (*Pf*, prefrontal; *F*, frontal; *P*, parietal, and *O*, occipital). Patient grounded at chin.

At *A*, patient ceased voluntary movements, opened eyes, and gazed fixedly at camera. He did not answer questions or otherwise react to sound stimuli. At *C*, patient made tasting, swallowing, and chewing movements. At *D*, he touched chin electrode while continuing these movements. At *E*, when his hands were removed from his face, he crossed his arms on his chest. At *F*, voluntary movements began after signs of displeasure on realizing an attack had taken place.

psychomotor. Before the EEG examination was made, it was thought that the absences, like the automatisms, were of temporal origin and that the attacks of grand mal were the result of an excessive spread of the discharge.

The interictal EEG, taken while awake or during hyperpnea, showed paroxysmal abnormalities with the characteristic appearance of petit mal epilepsy, i. e., discharges composed

of spike-and-wave complexes, repeated with a frequency of three per second and appearing suddenly in both hemispheres symmetrically and synchronously from the beginning and spreading rapidly to all areas of both hemispheres without using the mechanisms of transcortical propagation used by focal epileptic discharges.

In view of these unsuspected findings, we decided to make simultaneous films of the clinical attacks and of the EEG records in order to see whether the abnormalities of the latter changed on passing from a pure absence to an absence with coordinated motor activity (automatism).†

The attacks were brought on by means of hyperpnea. So as to make the motor abnormalities during the fits more evident, the patient was directed to carry out voluntary movements synchronized with the breathing movements during hyperpnea. Or he was asked to count the inspirations aloud and on his fingers. Thus, it was possible to see clearly the moment when the patient's mental or voluntary motor activity was interrupted. Consciousness was explored by means of auditory and painful stimuli at regular intervals.

RESULTS

The EEG obtained under these conditions showed only the abnormalities which are characteristics of petit mal epilepsy (Figure).

With different degrees of hyperpnea the EEG discharges were of varying duration, while the clinical manifestations were of diverse types. In larval attacks voluntary movements became slightly slower and clumsy, while counting was badly articulated and showed scanning speech.

With deeper hyperpnea, the intensity of the attacks became greater, and voluntary movements were interrupted for a short time with loss of consciousness and with or without blinking and nodding, this last occurring rhythmically with the spike-and-wave rhythm of the EEG. At other times, the attacks were even severer, and the patient ceased voluntary movements, became unconscious, stared, and acted with more or less complex automatisms.

In one case the patient crossed his arms on his chest, touched the chin electrode, swallowed several times, smacked his lips, nodded, blinked, placed his hands between his legs, and carefully creased his trousers. The end of the attack was sudden, and the patient was displeased to find himself in a position which showed he had had a fit. Major and minor attacks disappeared, and EEG discharges began before clinical symptoms, thus giving us time to start filming.

COMMENT

At variance with the original point of view stated in previous studies,‡ in 1949 Fuster [1] admitted the possibility that some psychomotor attacks might be produced by an epileptogenic discharge originating outside the temporal lobes in subcortical structures intimately related with them.

The subcortical origin of certain psychomotor attacks had long been suspected because of the electroencephalographic features in interictal records in some cases in which no evidence of lateralization was obtained, even in nasopharyngeal records.§

† A 16-mm. film showing the simultaneous record of the attacks and the EEG abnormalities was presented with this paper.

‡ References 3 through 5.

§ References 3 and 4.

Furthermore, ictal records of Hill,[6] and also of Jasper and co-workers,[9] have shown that temporal areas were only trigger zones and that subcortical structures were really responsible for ictal automatisms. In fact, in the experience of Jasper, the temporal automatisms started after the epileptogenic discharge originating in one temporal lobe became bisynchronous, a finding which was interpreted as the activation of the subcortical structures. By that time the temporal discharge might have disappeared, and also the record might have been silent in both temporal lobes.

On the other hand, various authors || have remarked that, in spite of ictal automatisms being due in the largest percentage to a discharge originating in the temporal lobe, they may be set in motion in some cases by discharges from the silent areas of the frontal lobe. Unfortunately, there were no ictal records on such cases.

Our recent ictal records have confirmed Jasper's studies in cases of ictal automatisms of unilateral temporal origin, but we have not succeeded in obtaining an ictal record of automatisms with bisynchronous temporal discharges from the very beginning; i. e., there was no evidence of ictal automatisms due to a discharge starting primarily in subcortical structures. We believe that the cases reported here give proof of that, inasmuch as typical psychomotor attacks, identical with those produced by a temporal discharge, were accompanied by a petit mal rhythm in the ictal EEG, i. e., by discharges which, in accordance with present knowledge, are due to the epileptiform activation of one or more diencephalic areas.

In both cases studied, whether the patient had an absence or an elaborated automatism or passed gradually from one to the other, it was impossible to observe any change in the petit mal type of the EEG discharges, whether in the frequency or in the shape of the complexes or in their topography. Thus, there was no evidence that the discharge would have spread to other structures, and for this reason we can assume that absences and automatisms were determined only by epileptic activation of these diencephalic structures.

In ictal records of Hill,[6] the results differed from those of Jasper [9] in the sense that Hill found that when the epileptic discharge originating in temporal lobes became bisynchronous, the loss of consciousness started but the automatisms did not begin until the EEG discharge was over. Those results caused Hill to admit that the clinically ictal automatisms were really postictal and that ictal manifestations were only absences. The statement was only for the automatisms, in which he had opportunity to record ictal discharges, but he said: "True epileptic automatism-coordinated behavior during the bilateral discharge in the brain has not been observed in the present series. The writer doubts whether it ever occurs." On the contrary, our two cases of primary automatisms with ictal petit mal discharges prove that at least some cases of ictal automatisms are of ictal mechanism. As the type of discharge is different from the discharges seen in cases of ictal automatisms with bisynchronous temporal discharges, either primary or secondary to a unilateral temporal discharge, we must suppose that the structures activated in our two cases were different from those activated in the former studies.

We wish to emphasize that we do not state that these diencephalic structures are psychomotor; we mean, rather, that a discharge originating in them may set

|| References 6 and 7.

ictal automatisms in motion. At the present time there is no evidence to indicate whether they are of psychomotor or psychoparetic mechanism. For this reason, we prefer to use the term ictal automatisms instead of psychoparetic or psychomotor attacks. The term ictal automatism has the advantage of being merely descriptive of the facts, without entering into doubtful physiopathological interpretations.

It should be pointed out that in the two cases here reported, the pattern of automatisms was like those we have called primary automatism.[2] In this type automatisms are not preceded by any aura or corticofocal phenomena. They are of the same type as those originating in silent cortical temporal or frontal areas. They alternated with absences and primary grand mal, two types of attacks which Penfield [10] has described as appearing in epilepsy from silent cortical and subcortical areas. But there were no unconscious contraversive attacks. Therefore, any automatisms set in motion by a discharge from such structures will have the characteristics of an ictal automatism due to a discharge from the silent areas of the temporal lobe (primary automatisms or automatisms secondary to an epigastric or cephalic aura). The sequence of events in these cases would also be the same as that in ictal automatisms due to an epileptogenic discharge from silent areas of the frontal cortex.

In secondary automatisms (or secondary psychomotor attacks), as in secondary grand mal attacks (focal grand mal of other authors), the pattern of the attack or the sequence of the first phenomena let us establish in most cases the seat of the epileptogenic focus. For instance, an initial visual hallucinatory phenomenon points to the posterior part of the temporal lobe; an aphasic one, to the left temporoparietal region in a right-handed patient, and an olfactory one, to the uncus or its neighboring regions, either in the mesial part of the temporal lobe or in the orbitofrontal region.

But in cases of primary psychomotor attacks, or some secondary ones preceded only by cephalic or epigastric auras, we cannot predict where the epileptogenic focus is on the basis of the pattern of the automatisms. In these cases there is still the possibility that the apparently primary ictal automatism could be a secondary one in which the first corticofocal phenomena are masked by retrograde amnesia (pseudoprimary psychomotor attacks).

Clinically there is no way to distinguish between a true primary psychomotor attack and a pseudoprimary one. Sometimes, after careful questioning of the patient, searching for the characteristics of the minor attacks during sleep or after intensive medication, the first corticofocal phenomena may appear, permitting the establishment of the pattern of a secondary automatism. But in negative cases doubt persists. The only way in which to make a sure diagnosis in these cases is by using the EEG, which will show the position of the epileptiform focus. This will be in a known cortical area, in the case of a secondary automatism, or in one of the silent cortical or subcortical areas, in the case of a true primary psychomotor attack.

Even in the event that one could diagnose the true primary psychomotor attacks, there would be no way of telling the pattern of the automatism, or of determining in which of the three silent areas the epileptogenic focus could be; that could be determined only by using the EEG.

CONCLUSIONS AND SUMMARY

Typical primary ictal automatisms (primary psychomotor attacks) identical with those seen in epilepsy originating in the temporal and frontal silent areas were recorded (filmed) simultaneously with EEG discharges of the type usually associated with the petit mal epilepsy.

As these EEG abnormalities represent the epileptiform activation of diencephalic structures, it is supposed that the clinically primary automatisms may be the result of epileptic discharges originating not only in the silent temporal areas, but also in diencephalic structures responsible for the clinical and electroencephalographic features of petit mal epilepsy.

Although these automatisms were really ictal, there was no evidence to indicate whether they were of psychoparetic or psychomotor mechanism. We thus prefer to continue calling them ictal automatisms, which is a good descriptive term.

Although this work refers to the subcortical structures responsible for the petit mal epilepsy, the possibility is not ruled out that other silent subcortical areas may likewise be the seat of epileptogenic discharges capable of producing similar automatisms. This is especially possible for those subcortical structures related to the temporal lobes.

At the present time, we may say that clinically primary ictal automatisms can be set in motion by epileptic discharges originating in silent cortical areas (temporal and frontal) and in subcortical silent areas—some related to the temporal lobes and others responsible for the petit mal attacks.

Ictal records show that discharges originating in temporal silent areas produced automatisms only after secondary activation of the subcortical structures. We have not confirmed this mechanism for automatisms of frontal origin.

The types of automatisms in our two cases were of the primary type, similar to those set in motion by epileptic discharges from silent temporal or frontal cortical areas. They alternated also with absences and primary grand mal attacks, two types of attacks usually seen in epilepsy originating in silent cortical or subcortical areas.

Attacks of absences and primary grand mal, and automatisms of the primary type may be due to epileptic discharges from silent cortical (temporal and frontal) and subcortical areas.

Meanwhile, in cases of automatisms preceded by auras or any known cortico-focal manifestations, the pattern led us to diagnose the site of the epileptogenic focus; in the case of the primary automatisms, like those suffered by our patients, the localization is possible only with the EEG.

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INFLUENCE OF SEX AND AGE ON CONVULSIONS INDUCED BY ELECTRIC SHOCK TREATMENT

G. HOLMBERG, M.D.
STOCKHOLM, SWEDEN

WITH A view to elucidating the influence of different factors on the duration and intensity of an epileptic seizure and on the frequency of the clonic jerks, I have previously investigated the effect, *inter alia*, of the administration of oxygen (Holmberg [1]). In the present article the influence of sex and age factors will be considered. Watterson [2] found that the stimulus threshold for electrically induced epileptic seizures rises with increasing age. Kalinowsky [3] observed that the stimulus threshold was higher when the patients were more advanced in age, and that the threshold was higher for men than for women. I have not been able to find that any investigation of the influence of age and sex factors on the duration and intensity of the convulsions is mentioned in the literature.

TABLE 1.—*Distribution of the Material According to Age and Sex*

	Less Than 30 Years	30-39 Years	Greater Than 39 Years	Total
Men	14	10	13	37
Women	18	26	18	62
Total	32	36	31	99

METHOD AND MATERIAL

A special electromyographic method was employed for recording the convulsions (Holmberg [1]). By means of the recordings it was possible to measure the duration of the tonic and clonic phases, the relative intensity of the convulsions, and the frequency of the clonic jerks. In order to determine the intensity of the convulsions and the frequency of the clonic jerks at the different parts of the seizure, the recordings were divided into periods of five seconds.*

The material consisted of recordings from 99 patients ranging in age from 19 to 64 years. The distribution of age and sex is shown in Table 1. Routine shock treatments were administered. The first shock in a series of treatments was never included, as it usually has a greater intensity than the subsequent shocks.

RESULTS

A. *Influence of Sex.*—The influence of the sex factors on the convulsions is shown in Table 2.

The Table shows that the duration of the convulsions was much the same for men and women, as regards both the tonic and the clonic phase. No significant difference could be observed.

From the Psychiatric Clinic of the Royal Caroline Medicosurgical Institute; Chief, Prof. T. Sjögren.

* The time was measured in seconds and the intensity in arbitrary units.

The greatest intensity reached during any period of the seizure (the peak intensity) was higher for men than for women, and the difference was significant. The figures were 6.78 ± 0.189 for men, and 6.09 ± 0.173 for women; $t = 2.691$; $df = 97$; $P < 0.01$.

The frequency of the clonic jerks (number of jerks per five-second period) was higher throughout for women than for men. For the first part of the clonic phase (15 to 20 seconds after the initiation of the seizure) the difference was almost significant. The figures were 16.48 ± 0.551 for men, and 18.78 ± 0.408 for women; $t = 2.585$; $P < 0.05$. The difference was almost significant also for the next five-

TABLE 2.—*Influence of Sex on Convulsions Induced by Electric Shock Treatment*

	Men	Women	Total
Tonus duration	13.4	13.7	13.6
Clonus duration	24.2	24.1	24.2
Total duration	37.6	37.8	37.8
Peak intensity	**6.78**	**6.09**	6.35
Frequency of clonic jerks			
15-20 sec. period	**16.5**	**18.8**	17.9
20-25 sec. period	**14.5**	**15.7**	15.3
25-30 sec. period	11.1	12.8	12.2

TABLE 3.—*Influence of Age on Convulsions Induced by Electric Shock Treatment*

	< 30 Years	30-39 Years	> 39 Years
Tonus duration	**12.8**	**14.0**	14.0
Clonus duration	24.7	24.1	23.8
Total duration	37.5	38.1	37.8
Peak intensity	**6.90**	6.21	**5.95**
Frequency of clonic jerks			
15-20 sec. period	18.3	**18.7**	**16.6**
20-25 sec. period	15.0	15.9	14.7
25-30 sec. period	12.2	12.7	11.5

second period; $t = 2.323$. When the t values are added together for the differences during the two time periods according to the formula

$$T = \frac{t_1 + t_2}{\sqrt{2}},$$

then $T = 3.471$ and $P < 0.001$. This confirms that the clonus frequency is significantly higher in women.

B. *Influence of Age.*—Table 3 shows the influence of age on the convulsions. Significance was calculated only when the primary numbers seemed to differ. The means that were compared statistically appear in boldface in the Table.

The total duration of the convulsions varied only inconsiderably, while the duration of the tonic phase appeared to be somewhat greater for the intermediate group as compared with the younger group, and the duration of the clonic phase seemed to decrease slightly in accordance with increasing age. The tonic phase was (not significantly) shorter for the youngest patients. It should be pointed out, however, that this difference was restricted to the women.

The intensity of the convulsion was less for patients of a more advanced age. The difference between the lowest and the highest age groups was significant. The figures were 6.90 ± 0.228 and 5.95 ± 0.228, respectively; $t = 2.946$; $df = 61$; $P < 0.01$.

The frequency of the clonic jerks appeared to be somewhat higher for the intermediate group than for the lower age group, while the highest age group was found to have the lowest frequency. The difference between the intermediate group and the highest age group was nearly significant. Calculations were made only for the first part of the clonic phase. For the age group between 30 and 39 years the figures were 18.68 ± 0.546, and for the age group over 39 years it was 16.60 ± 0.705; $t = 2.334$; $df = 54$; $P < 0.05$.

COMMENT

Perhaps the most noteworthy feature of this investigation was the striking constancy of the duration of the induced epileptic seizures regardless of sex and age.

The intensity of the convulsions was greater for men than for women and decreased with advancing age. The frequency of the clonic jerks was almost significantly higher for women than for men. The same observation was made before (Holmberg [1]). This may probably be attributed to differences in the delicacy of structures of the central nervous system. According to Jung,[4] it seems that the frequency of the clonic jerks is determined by the striatum. It can be observed on the electroencephalogram that women in general appear to have a higher frequency of alpha waves, and that spike-and-wave discharges are also more rapid for women than for men. Even if this may be a question of diencephalic phenomena, there is probably a general morphological connection between this and the higher frequency of the clonic jerks in the case of women.

Both the frequency of the clonic jerks and the intensity of the convulsions decreased with increasing age, but the former was highest for the intermediate age group, a fact that is difficult to explain. The decrease with advancing age is probably connected with decreasing cerebral excitability, an observation which has also been made by other investigators.

SUMMARY

A special electromyographic method was employed for an investigation of the influence of sex and age factors on convulsions induced by electric shock treatment, and the following are the main results obtained:

1. The duration of the convulsions and the relation between the duration of the tonic and that of the clonic phase showed a remarkable degree of constancy and were to a great extent independent of age and sex. The tonic phase was, however, somewhat shorter for young women than for other persons.

2. The intensity of the convulsions was lower for women than for men, but the frequency of the clonic jerks was higher for women than for men. This is assumed to depend on a general morphological difference in the nervous system.

3. The intensity of the convulsions was less at a more advanced age. The frequency of the clonic jerks was highest for the age group between 30 and 39 years and showed a tendency to decrease with advancing age; this applies especially to men. The general decrease with increasing age is assumed to be connected with a lowering of cerebral excitability.

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EXPERIMENTAL OBSERVATIONS CONCERNING CEREBRAL ANGIOGRAPHY

KENNETH M. BROWNE, M.D.
AND
W. EUGENE STERN, M.D.
BALTIMORE

AN UNUSUAL opportunity for studying the intracranial and extracranial circulations simultaneously was afforded by a perfusion method of angiography in the cat, using the vertex-base x-ray projection. By this technique the entire circle of Willis, as well as its main afferent and efferent branches, could be visualized roentgenographically together with much of the extracranial carotid system. It was thus possible to make certain observations of general interest concerning the cerebral circulation and of particular interest in regard to some etiologic factors concerned with neurologic sequelae of carotid angiography. The technique of photomicrography was also utilized in order to include pial arteries in this study.

METHODS

Carotid Angiography.—A total of 220 angiographic studies were performed on 14 cats, with 10% colloidal suspension of thorium dioxide (Thorotrast) used as the contrast medium in all but 2 experiments, in which 35% iodopyracet (Diodrast) was employed. The common carotid artery was cannulated with a plastic tube, and the contrast medium was delivered to it by a compressed air system which incorporated a reducing valve, so that the injection pressures were controllable and reproducible. Injection pressures of 660 to 750 mm. Hg were usually necessary to fill the circle of Willis against the blood pressures encountered in these experiments.* Eleven cats were immobilized with purified Chondodendron tomentosum extract (Intocostrin), and 3 were anesthetized with intravenous pentobarbital sodium. In either case artificial respiration was employed except in one experiment. Operative procedures were carried out under local anesthesia with 1% procaine hydrochloride in the unanesthetized cats. X-ray factors were as follows: tube-film distance 48 cm.; exposure time 3.5 seconds; 10 ma.; 65 kv.; cardboard cassettes. The period of the injection of the contrast medium coincided exactly with the x-ray

National Research Council Fellow (Dr. Stern).

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From the Division of Neurological Surgery, The Johns Hopkins University School of Medicine.

*Carotid Circulation: The carotid circulation in the cat differs from that of man. After embryonic life the internal carotid artery is a vestigial cord which does not remain patent for more than a few millimeters distal to its origin. The main source of arterial blood from the common carotid artery is by way of the external carotid artery, which continues as the internal maxillary artery to the pterygoid fossa. Here the artery divides into a great many thin-walled vessels, 0.2 to 0.3 mm. in diameter, to form the external rete. Several arteries which arise from the external rete course posteriorly and superiorly through the orbital fissure to the cavernous sinus, where they give origin to a second rete. Emerging from this internal rete is a single, large artery, known as the anastomotic artery, which joins the distal extremity of the rudimentary internal carotid artery and gives origin to the anterior portion of the circle of Willis, together with the anterior and middle cerebral arteries.

exposure interval of 3.5 seconds, during which time 2 to 5 cc. of dye was injected. A total of 24 electrical excitations of the cervical sympathetic trunk were done in eight cats with a thyratron type stimulator. Excitatory stimuli varied from 2 to 10 volts at a 60-cycle frequency and from 3 to 5 volts at a 240-cycle frequency. The duration of the stimulus was between 5 and 300 seconds. A continuous blood pressure recording from the femoral artery was made in each experiment.

Pial Artery Photography.—Microscopic observations of pial arteries were carried out in 10 cats with purified Chondodendron tomentosum extract immobilization and local anesthesia, respiration being maintained artificially. Pial arteries were viewed through a parietal trephine opening, with the dura reflected and the pia-arachnoid covered with warm white oil. Photographs and visual observations were made of pial arteries at a magnification of about × 33 before, during, and after (*a*) the intracarotid injection of air, (*b*) the stretching, pinching, and electrical stimulation of the carotid artery, and (*c*) the intracarotid injection of 35% and 70% iodopyracet, as well as a 0.1 N solution of sodium chloride. The blood pressure was recorded continuously during these observations.

OBSERVATIONS

Arterial Spasm.—The simultaneous roentgenologic visualization of the intracranial and extracranial arterial systems afforded an opportunity to compare the incidence of arterial spasm in the extracranial and in the intracranial arteries. It also allowed examination of the hypothesis that spasm in an extracranial branch of the carotid artery may reflexly induce spasm in some part of the intracranial circulation.

Two types of arterial constriction were seen in the extracranial branches of the carotid artery. The commonest type was a diffuse narrowing, usually involving the entire length of an artery, such as the lingual artery (Fig. 1). Such a change was observed 38 times in 220 arteriograms, most of which were made with Thorotrast. This generalized constriction frequently involved only one extracranial artery visualized in the arteriogram and characteristically would be present in one arteriogram and not in the next, thus indicating that the change was transient in nature. This arterial constriction was observed in animals under general anesthesia (Fig. 1). It was not prevented by section of the ipsilateral sympathetic trunk. A similar spontaneous narrowing of one portion of an intracranial artery was not observed.

The second type of arterial constriction seen in the extracranial carotid circulation in association with carotid angiography consisted of one or more focal areas of intense arterial spasm. Such dramatic instances of arterial spasm were seen only after the intravenous or intra-arterial injection of histamine or epinephrine (Fig. 2). In each such instance the contrast medium was Thorotrast. These focal regions of arterial spasm were characterized by their sharply delimited margins and by their occurrence at a particular site in successive arteriograms over periods as long as 10 minutes. This fact suggested that they were persistent from one arteriogram to the next, though of course they may have been incited by each injection and may have disappeared between injections. A similar type of intense, focal arterial spasm was not observed in the intracranial circulation in any of the angiograms. There was no apparent reflex change in the caliber of large intracranial arteries at the base of the brain as a result of focal arterial spasm in the extracranial circulation.

Such evidences of arterial spasm as those described above were not observed in the intracranial arteries in angiograms; however, generalized and symmetrical changes in the caliber of intracranial arteries did take place under certain circum-

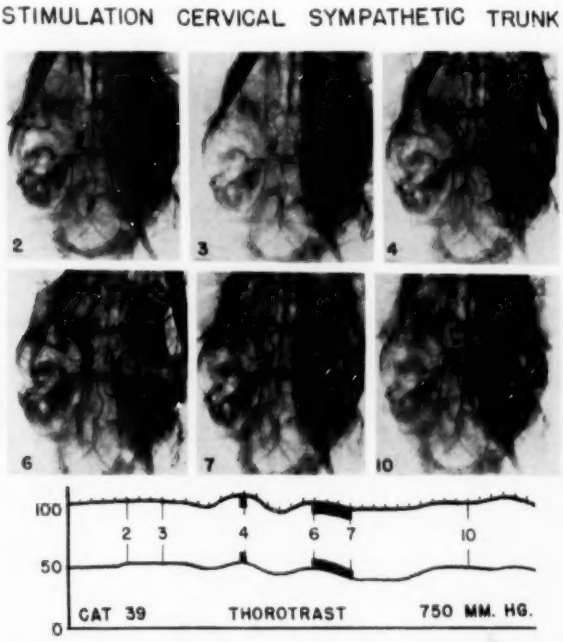

Fig. 1.—The common carotid artery on the right side of the figures was injected with 10% colloidal thorium dioxide (Thorotrast) under 750 mm. Hg pressure, and the ipsilateral sympathetic trunk was stimulated, as indicated by the solid bars on the blood pressure curve. The cat was anesthetized with pentobarbital sodium. The numbers on the blood pressure record indicate the time at which the above arteriograms were made, and the vertical marks indicate one-minute intervals. The arterial shunting effect is fully developed in arteriogram 6. Notice the diffuse constriction of the lingual artery in arteriograms 2, 4, and 7.

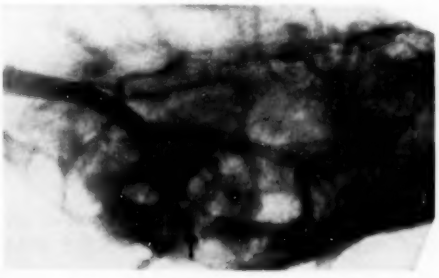

Fig. 2.—A severe degree of constriction of the external maxillary artery is indicated by the arrow. It developed 1 minute after the intracarotid injection of 0.5 mg. of histamine base and was present at the same site in several arteriograms made in the next 10 minutes. The contrast medium was 10% colloidal thorium dioxide, injected at a pressure of 300 mm. Hg, with the cat under local anesthesia and curare immobilization.

stances. For example, it was observed that large intracranial arteries at the base of the brain dilated passively, subsequent to sudden increases in the systemic blood pressure induced by histamine or epinephrine. Conversely, they narrowed markedly during cardiac arrest at the end of several minutes of asphyxia (Fig. 3). It

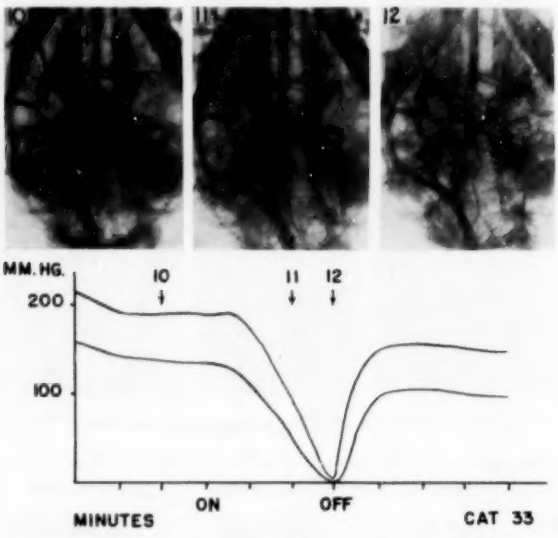

Fig. 3.—The marked narrowing of intracranial arteries which takes place with cardiac arrest after four minutes of asphyxia in a cat under local anesthesia and curare immobilization is illustrated. Note the decrease in the tortuosity of the basilar artery during cardiac arrest.

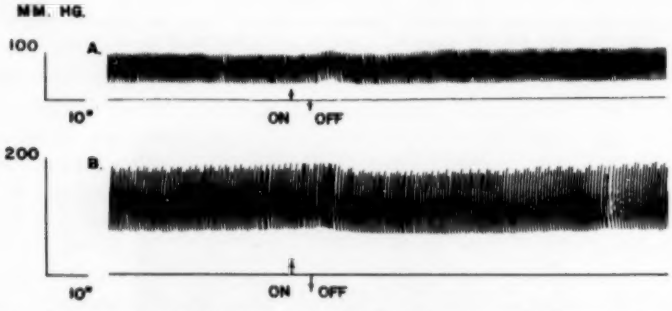

Fig. 4.—The intracarotid injection of 3 to 5 cc. of Thorotrast or iodopyracet under pressures up to 750 mm. Hg failed to elicit a notable carotid sinus reflex in cats under either general (*A*) or local (*B*) anesthesia.

was also of interest to note that the degree of tortuosity of the basilar artery was diminished in shock states, as compared with its course when the blood pressure was at hypertensive levels (Fig. 3).

Electrical Stimulation of the Cervical Sympathetic Trunk.—Results of unilateral electrical stimulation of a cervical sympathetic trunk upon the intracranial and extracranial blood flow in the cat, as evidenced in angiograms, have previously been

reported.[1] In 50% of such experiments there occurred a shunting of blood from the extracranial to the intracranial circulation. A passive dilatation of that portion of the circle of Willis contralateral to the stimulation occurred in response to the intracranial diversion of extracranial blood flow, but ipsilateral arteries at the base resisted this passive dilatation, presumably because their tone was increased as the result of the stimulation of the cervical sympathetic trunk. The resulting asym-

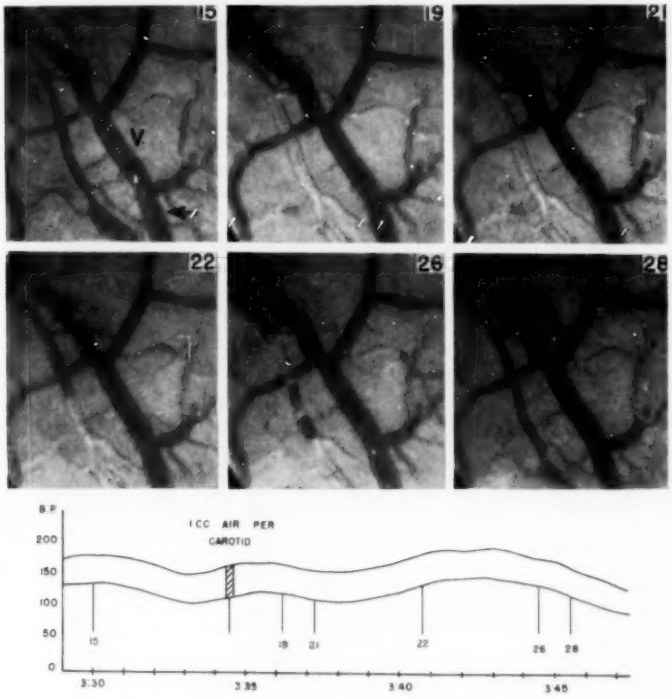

Fig. 5.—The times at which the photomicrographs of pial vessels were made are indicated on the blood pressure curve. *A*, pial artery; *V*, pial vein. Photomicrograph 15 illustrates streamline flow in a cortical vein during the intracarotid injection of isotonic saline. Photomicrographs 19 and 21 demonstrate the translucency of pial arteries when filled with air. Note the dilatation of the air-filled pial artery. In photographs 22 and 26 air is being forced out of the pial artery by the blood column. Note the absence of subsequent arterial spasm in photograph 28. About × 33.

metry in caliber of the corresponding lateral halves of the circle of Willis was readily apparent on the poststimulation angiograms (Fig. 1). Such an asymmetry of the circle of Willis was not seen after sectioning one cervical sympathetic trunk.

An examination of more than 150 angiograms made with both sympathetic trunks intact revealed no instance of asymmetry of the circle of Willis similar to that observed in 50% of the stimulations of the cervical sympathetic chain. We were unable, therefore, to obtain any arteriographic evidence that angiography performed in the cat by the method described for these experiments was associated with direct

or reflex excitation of the fibers in the cervical sympathetic trunk ipsilateral to the injection with either local or general anesthesia, using 35% iodopyracet or Thorotrast.

The Carotid Sinus Reflex.—No evidence for the elicitation of the carotid sinus reflex was noted in 220 arteriographic studies performed in 14 cats. Continuous records of pulse rate and pulse volume, as well as of the systolic and diastolic blood pressures, failed to evidence more than minimal changes in these values, even in the

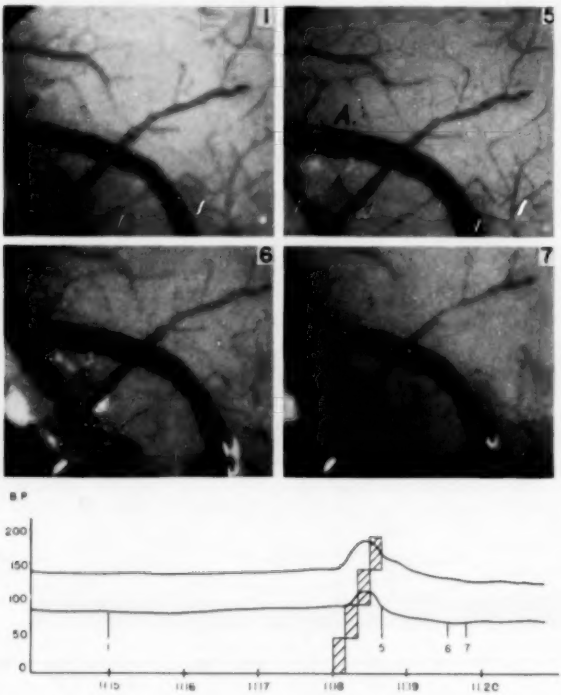

Fig. 6.—A 35% solution of iodopyracet (Diodrast) was injected into the common carotid artery at 1 cc. increments, as indicated on the blood pressure curve by the diagonally lined blocks. Times at which the photomicrographs of pial vessels were made are also indicated on the curve. The marked dilatation of a parietal pial artery ipsilateral to the injection is evident in the postinjection photographs. About × 33.

63 angiograms made without injecting a local anesthetic agent in the carotid sinus region (Fig. 4). No evidence was obtained to support the hypothesis that the carotid sinus may be sensitive to iodopyracet.[2] The gradual but marked falls in blood pressure which followed repeated intracarotid injections of 35% iodopyracet were probably the result of the direct vasodilatory effect of iodopyracet upon the peripheral blood vessels.[3]

PIAL ARTERY MICROSCOPY

Isotonic Saline Injection.—In order to determine the effect of iodopyracet on intracranial arterioles, direct microscopic observations of pial vessels was carried out in cats. Control injections of a 0.1 N solution of NaCl into the common caro-

tid artery resulted in no significant alterations in the caliber of ipsilateral pial arteries. When the injection was made in such volume and at such a rate as entirely to displace the blood within the pial artery, the artery became translucent; or if the injection was somewhat irregular in rate, the artery would alternately disappear and reappear from view, as observed through the microscope. Gross observation of the cortex at such times gave the appearance of blanching. Such a phenomenon

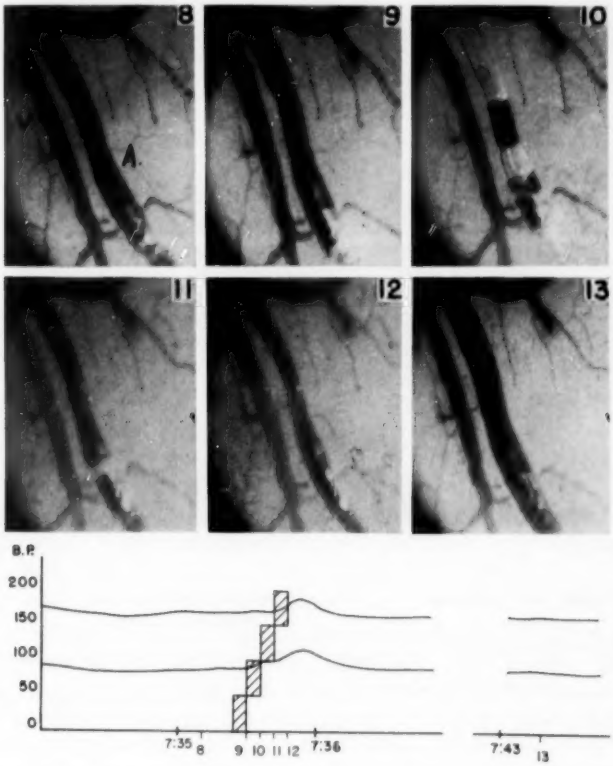

Fig. 7.—An instance of severe pial artery constriction subsequent to the slow injection of 4 cc. of 35% iodopyracet in a cat under local anesthesia is illustrated. The air emboli seen in photograph 10 came from bubbles in the iodopyracet caused by agitating the dye and rapidly passed through the pial artery. About × 33.

was not the result of vasoconstriction. Rather, it was caused by a variable degree of replacement of the pial blood by the colorless injection material. In our experience, when the phenomenon of blanching of the cortex was observed during the intracarotid injection of either 35% or 70% iodopyracet, it was the result of the above mechanism, rather than being caused by a sudden, severe vasoconstriction, as reported by others.[4] This color contrast between the injected solution and blood allowed the demonstration of "streamline flow" in cortical veins (Fig. 5, photograph 15).

Intracarotid Iodopyracet.—The intracarotid injection of 35% and 70% iodopyracet at room temperature resulted in dilatation of the pial artery under observation during and for one to several minutes after the completion of the injection in 9 out of 10 instances. Dilatation of a pial artery during and subsequent to the continuous intracarotid injection of 4 cc. of 35% iodopyracet at a rate of 1 cc. every 10

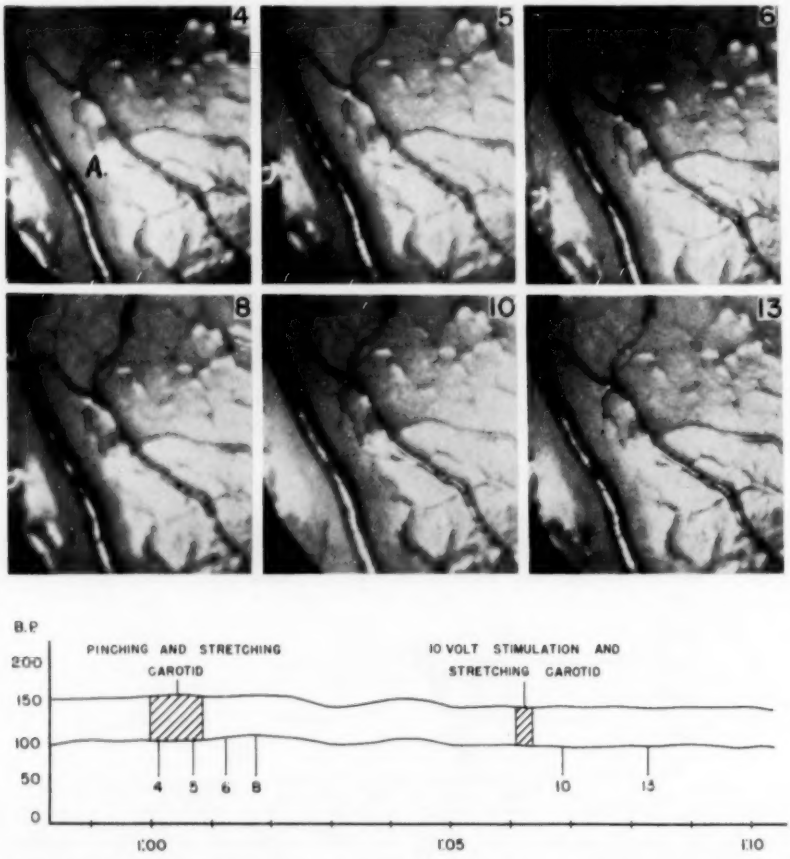

Fig. 8.—Pinching, stretching, and electrically stimulating the common carotid artery of a cat under local anesthesia failed to induce spasm of an ipsilateral parietal pial artery.

seconds is illustrated in Figure 6. The greatest dilatation of the artery took place at the end of the injection, when the systolic and diastolic blood pressures had risen sharply; but it persisted to a less degree one minute thereafter, when the blood pressure had fallen to control levels. This response to iodopyracet is similar to that usually seen in extracranial arterioles ipsilateral to the intracarotid injection of the dye in man. Although vasodilatation was the rule in pial arteries under the conditions of our experiments, marked vasoconstriction of a pial artery was also noted in association with the ipsilateral intracarotid injection of 35% iodopyracet on one occasion (Fig. 7). Although the true incidence of that response would only be

determined by hundreds of injections with various batches of dye, at least the fact that it may occur has been photographically recorded. The vasoconstriction was transient, and it took place in association with a moderate elevation in the systolic and diastolic blood pressures. In this example, a few bubbles of air flashed through the pial artery during the iodopyracet injection. There can be little doubt that the vasoconstriction was the result of the iodopyracet rather than the air emboli, because, in agreement with the extensive studies of Villaret and Cachera,[5] we did not observe that air emboli alone ever caused pial arterial spasm.

Intracarotid Air.—Not infrequently air emboli were noted when a pial artery was being observed microscopically during the various intracarotid injections made in this study. Bubbles of air, resulting from agitation of the injected material, appeared as air emboli in pial arteries. The accidental intracarotid injection of such small amounts of air usually resulted in air emboli that flashed through the pial artery so rapidly that they could not readily be photographed by the single exposure technique, but occasionally they were photographed by chance (Fig. 7).

When 1 to 2 cc. quantities of air were injected into the carotid artery, the pial artery under observation was filled with air. The air embolus in such instances was observed to exclude blood flow in all pial arteries in the microscopic field for as long as 10 minutes (Fig. 5). Pial arteries thus filled with air tended to dilate until the embolus passed on. Then the artery promptly returned to its control caliber without intervening or subsequent "spasm." Even when the air embolus occupied only a small segment of the pial artery, that portion of the vessel seemed to dilate (Fig. 7).

In order to determine whether manipulation of the carotid artery would initiate reflex spasm of pial arteries, pial artery microscopy was carried out as the carotid artery was stimulated electrically or as it was intermittently stretched and pinched repeatedly in one experiment. Constriction of ipsilateral pial arteries was not observed. Either no effect was apparent or a slight dilatation of the observed pial artery took place (Fig. 8).

COMMENT

The term arterial "spasm" implies a severe constriction of the arterial lumen not ordinarily apparent under physiologic conditions. Such a degree of vasoconstriction has been so commonly met with in the extracranial circulation under various circumstances that there can be no doubt as to its existence. On the other hand, the concept that intracranial arterial spasm may exist has met with considerable skepticism.[6] In part this is true because certain clinical and angiographic phenomena have been attributed to spasm of cerebral arteries without definite proof of that contention.

Angiographic changes of two types were considered consistent with the interpretation of arterial spasm in this study: (1) a focal area of intense constriction seen in an artery which was well filled proximal and distal to that segment and (2) a diffuse arterial narrowing occurring in an artery so situated in the injected system of vessels as to be proximal to other arteries which were well filled. Subject to these criteria, the only instances of arterial spasm observed in the 220 arteriograms of this study occurred in the extracranial carotid system. It was therefore concluded that in the cat large extracranial branches of the carotid artery were more liable to arterial spasm under the conditions of our experiments than were the large intracranial arteries visualized by angiography.

These experiments gave no clear indication that local infiltration of the carotid artery at the site of the injection, general anesthesia, or ipsilateral division of the cervical sympathetic trunk influenced the development or release of extracranial arterial spasm which occurred distal to the injection site. It therefore seems possible that such arterial spasm was dependent upon some intrinsic response of the involved vessels, either as a result of a sudden stretch stimulus induced by the pressure injection or because of a local irritation of the vessel by the Thorotrast.

An objection to the concept that intracranial arterial spasm may occur during angiography has been succinctly stated by Ayer,[6] who pointed out that the relative lack of a well-developed media and the sparse character of the innervation of intracranial arteries would seem to make the possibility of these vessels being capable of spasm somewhat remote. However logical this reasoning, it is not in accord with experimental findings in a variety of animals. Direct visual and photographic observations of such spasm, even to the point of obliteration of the lumen, have been made regarding the basilar [7] and middle cerebral [8] arteries, as well as in the pial vessels over the cortex,[9] medulla,[7] and pons.[7] Indeed, the extensive studies of Villaret and Cachera [5] have demonstrated by direct photography of pial arteries in the dog that pial vessels evidence spasm persisting for weeks as the result of solid pial artery emboli. Thus, there would seem to be little reason for questioning the ability of intracranial arteries to constrict to the point of spasm in many animals. However, the reactivity of intracranial arteries in man remains to be more firmly established by systematic, direct observations. Although many persons experienced in the use of cerebral angiography feel confident that arterial spasm can be visualized roentgenologically on occasion, the possibility that other factors may be present and simulate spasm can seldom, if ever, be denied.

As previously mentioned, we observed no instance of arterial spasm of intracranial arteries large enough to be visualized in angiograms even after electrical stimulation of the cervical sympathetic trunk, but in one instance the intracarotid injection of 35% iodopyracet caused a transient constriction of a pial artery to 60% of its original caliber, as photographed through the microscope (Fig. 7).

It would seem to be clearly evident that in a variety of animals intracranial arteries, both large and small, are capable of true arterial spasm when stimulated directly. It is also evident in the cat that regional, less severe degrees of constriction of intracranial arteries may occur either during the intracarotid injection of iodopyracet or subsequent to electrical stimulation of the cervical sympathetic trunk. Marked changes in the intracranial circulation may thus result, even without presuming the occurrence of a severer, unphysiologic degree of constriction properly termed arterial spasm. It should be emphasized, however, that the vasolability of intracranial arteries varies considerably in different animal species, so that such results in animals cannot properly be applied to man.

SUMMARY

1. A method of perfusion angiography which allowed the simultaneous roentgenologic visualization of the intracranial and extracranial arteries in the cat demonstrated that a severe degree of arterial constriction occurred frequently in the extracranial portions of the carotid artery in the course of angiographic studies performed with Thorotrast.

2. Focal areas of marked arterial spasm were seen in the extracranial portions of the carotid artery after the intravenous or intracarotid injection of histamine or epinephrine.

3. Neither of the above changes in the extracranial arteries was associated with any apparent vasoconstriction of intracranial arteries large enough to be visualized in angiograms.

4. The only instances of asymmetry in the lateral halves of the circle of Willis occurred subsequent to the unilateral electrical stimulation of a cervical sympathetic trunk. The failure of a similar change to occur in the remaining angiograms thus failed to provide angiographic evidence that a reflex stimulation of the cervical sympathetic trunk occurred as the result of either manipulation of the carotid artery or the intracarotid injection of Thorotrast and iodopyracet (Diodrast).

5. The tortuosity of the basilar artery was increased with high systemic blood pressures and reduced when the animal was in shock.

6. Microscopic observations of pial arteries during carotid angiography indicated that the usual response of the pial arteries to 70 and 35% iodopyracet was an immediate but transient vasodilatation. However, the brief vasoconstriction of a pial artery subsequent to the intracarotid injection of 35% iodopyracet was also photographed.

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STUDY OF HUMAN CEREBRAL BIOPSY SPECIMENS IN AN ELECTRICALLY EXCITED CONDITION

H. McILWAIN, D.Sc., Ph.D.
LONDON, ENGLAND

MEANS of electrically stimulating the metabolism of separated cerebral tissues have recently been developed in these laboratories.* The methods render such tissue much more susceptible to a wide variety of agents than are unstimulated tissues,[3] and metabolic lesions, otherwise unapparent, may thus be detected. The methods are applicable to a few milligrams of tissue taken as biopsy specimens or during neurosurgical operations. They have not yet found a routine use, but their value in research is indicated by the following account, which describes briefly some results previously reported and adds others hitherto unpublished.

A separated fragment of the mammalian cerebral cortex is electrically inert when examined by techniques which reveal profuse and intricate electrical activity in the brain in situ. A few seconds only after such a fragment has been removed from the brain, not only will it give no electrical response to applied electrical pulses, but also the energy-rich substances which support such activity will largely have disappeared from the tissue. This emphasizes the close second-to-second dependence of cerebral activities on material supplied by the blood stream. In search for methods applicable to cerebral biopsy specimens, it was found that to a certain extent the blood stream could be replaced by oxygenated glucose salines, for thin fragments of cerebral tissues placed in such solutions resynthesized energy-rich intermediates.† For this reason their electrical excitability was reexamined under these circumstances.

Observation of electrical response in small fragments of tissue immersed in conducting saline solutions meets considerable difficulties, but this situation can be an excellent one for measurement of changes of metabolism. Metabolic and thermal responses to excitation in excised peripheral nerve tissues are well known and encouraged search for possible changes of this type in cerebral tissues. A variety of metabolic responses were soon clearly demonstrated.‡

From the Biochemical Laboratories, Institute of Psychiatry (British Postgraduate Medical Federation, University of London), Maudsley Hospital (S.E. 5).

Based on lectures given in September, 1953, at the National Institutes of Health and of Neurological Diseases and Blindness, Bethesda, Md., and at the New York State Psychiatric Institute.

* References 1 and 2.

† References 4 and 5.

‡ References 1, 2, 6, and 7.

EXPERIMENTAL STUDY

Specimens of human cerebral tissues § taken as soon as possible, usually within a minute, after cessation of blood flow to them were placed in small screw-capped bottles, cooled in ice water, and brought to the laboratory, where preparations for the experiment had already been made.‖ Selected portions of the tissue were chopped or sliced to fragments of 0.35 mm. or less in one dimension, but otherwise with minimal damage to cell structure. According to the type of experiment performed, 10 to 80 mg. of tissue was placed in each of a series of experimental vessels containing isotonic salines with various added substances. Adjacent portions were used in histological examinations.¶

The tissue in the experimental vessels was between electrodes to which were applied at chosen times electrical pulses of the time-voltage relationships described in individual experiments below. Respiration was measured continuously throughout the experiments, and at their termination samples were taken of fluid or tissue for determination of other products; further details are given elsewhere.#

EFFECTS OF APPLYING ELECTRICAL PULSES TO THE MORE NORMAL TISSUES

Respiratory Response.—Some 40 specimens have been examined which were from frontal or temporal lobectomy of cases in the majority of which the diagnosis

TABLE 1.—*Applied Electrical Pulses and the Metabolism, Normal and Abnormal Cerebral Tissues*

Tissue	Respiratory Rate (μmoles O_2/Gm./Hr.)		Lactic Acid Formation (μmoles/Gm./Hr.)	
	Without Pulses	With Pulses	Without Pulses	With Pulses
Gray matter from cerebral cortex, frontal region	57 ± 12 (20)	116 ± 11 (5)	27 ± 12 (8)	47 ± 12 (4)
Gray matter from cerebral cortex, temporal region	53 ± 13 (15)	98 ± 16 (4)	30 ± 11 (4)	62 ± 24 (4)
Subcortical white matter, frontal and temporal regions	25 ± 6 (5)	39 ± 9 (4)	21 ± 4 (4)	37 ± 14 (4)
Surrounding a glioma, occipital region	55, 57	61, 63	41	53
Surrounding an astrocytoma, frontal region	26, 24	26, 23	107	124

Tissues were examined as fragments in oxygenated glucose-phosphate saline in vessels with concentric electrodes. Those receiving pulses were first without them for 30 minutes; alternating condenser pulses of time constant 0.4 msec. were then applied at 100 per second for 30 minutes at a peak potential of 10 volts, then for 30 minutes at a peak potential of 18 volts, and then switched off while metabolism continued for a further 30 minutes. Lactic acid was determined at the end of the experiment. The respiratory rate with pulses which is quoted was that during their application at 18 volts; the lactic acid formation with pulses reflects the increase resulting from the hour's application of pulses at the two voltages quoted. Rates are calculated on the basis of the fresh tissue, with a dry weight found to be 17.9% of the fresh weight, and in the first three lines are followed by standard deviation, and in parentheses the number of specimens examined; others are individual values.

of psychomotor epilepsy or depression was made; further details have been cited.* No lesion in the actual specimens was evident to the unaided eye or microscopically, but caution remains necessary in regarding the tissues as normal. Results in Table 1 show that respiratory rates without applied pulses did not differ significantly between temporal and frontal regions, and in gray matter were similar to those found by other workers.† Variation among the present results, as represented by the standard deviation in Table 1, was greater than among comparable values for

§ Mr. Murray Falconer, Director Guy's-Maudsley Neurosurgical Unit, furnished human cerebral tissues.

‖ References 8 and 9.

¶ Dr. D. Naidoo, of this Institute, furnished the reports on certain of these.

References 1 through 10.

* References 8 and 9.

† References 11 through 14.

tissues from experimental animals.‡ It was of the same order of magnitude as variations in cerebral respiratory rate in vivo found by arterial-venous difference and rate of blood flow.[15] The respiratory rate of the subcortical white matter was some 45% of that of the cortical gray matter.

Respiratory rates in all the tissues examined could be approximately doubled by applied electrical pulses. Values are quoted in Table 1 which resulted from the application of pulses of characteristics found to give maximal response. This is the degree of increase which has been found also in cerebral tissues from experimental animals.§ The rates with applied pulses approximated those found for cerebral respiration in vivo by arterial-venous difference and rate of blood flow, while in the absence of pulses the rates observed were much lower.‖ This is consistent with the continuous electrical activity of the brain in vivo.

The respiratory response to applied pulses commenced within one or two minutes of their application, or possibly more promptly. It was maintained for an hour or so while they were applied and reverted promptly to its previous value when the pulses ceased.

Glycolytic Response.—Glycolysis, yielding lactic acid from glucose and representing the second main energy-yielding reaction of the brain, was also markedly increased by applied pulses. This is shown in Table 1, though the values there quoted do not represent the greatest rates which can be attained, as they give the effect of successive application of pulses which were submaximal and maximal.

Electrical Requirements for Response.—The magnitude of metabolic response given by cerebral tissues from laboratory animals to pulses of various electrical characteristics has been studied in detail.[16] Less information has been collected with human tissues, but the values available show interesting similarities to those of the pulses required to elicit responses when applied to electrodes at the brain in vivo.

Thus, with gray matter from the frontal lobe, condenser pulses of time-constant 0.4 msec. applied to electrodes 11 mm. apart afforded a small response at a 6-volt peak potential, and at 12 volts were approaching maximal response. The voltage gradient between the electrodes [10] was such that threshold was of the order of 0.35 volt per millimeter, and maximal response at about 0.9 volt per millimeter. When applied to the exposed cerebral hemispheres of a monkey, condenser pulses of time-constant 0.2 to 0.4 msec. with electrodes 3 to 8 mm. apart were found to be required at 5 to 20 volts for response.[17] Threshold for respiratory response in the separated cerebral tissue to sine-wave alternating currents of 50 cps with electrodes 2 mm. apart was less than 1.5 volts. Such currents at 60 cps applied to electrodes 1 mm. apart at the cortex of monkeys were required at 1 to 6 volts for excitation.[18] Threshold to sine-wave alternating currents in a specimen from the frontal lobe was lower at 100 cps than at 10 or 2,000 cps, a finding which, again, is analogous to observations in vivo.[19]

ABNORMAL TISSUES

Several observations have been made with material from tumors of cerebral tissues. Material from the center of such tumors has frequently shown, in agreement with a previous report,[20] low respiratory rates and high values for aerobic

‡ References 8 and 9.

§ References 1, 2, 6, and 7.

‖ References 8 and 9.

glycolysis. Response to applied pulses has been small or absent. More interesting is the behavior of tissues surrounding the core of the tumor, which respire more actively. Table 1 shows that tissue around a glioma may give in the absence of pulses rates for respiration and glycolysis which fall within normal ranges. In this case, applied pulses gave very little change in either respiration or glycolysis. Thus, electrical pulses in such experiments revealed abnormalities not seen in their absence.

Similarly, small response was seen in tissues surrounding an astrocytoma, though here the relatively high glycolytic rate indicated metabolic abnormality even in the absence of pulses. Lack of response in such tissues is presumably the counterpart in vitro of the absence of recordable potential changes in neoplastic tissues in vivo, though surrounding neurons may discharge abnormally. It would be especially interesting to examine threshold to stimulation in tissue from epileptogenic areas. Though some of the tissues examined have been of this type, they have not shown an appreciably different response to pulses giving maximal or submaximal response. Accurate determination of threshold has not yet been carried out.

ELECTRICAL PULSES AND EXPERIMENTALLY ALTERED TISSUES

Substrates.—Results described above have been obtained with tissues immersed in oxygenated isotonic salines with glucose as substrate, for it is almost exclusively glucose which performs this role in vivo. With separated human cerebral tissues, several other substrates are oxidized.¶ However, relatively few afford respiratory response to applied pulses,# and thus, again, stimulation introduces an element of specificity which makes the behavior of the separated tissue much more akin to the behavior of the brain in vivo. Only pyruvate and lactate replaced glucose in supporting generally the respiratory response; interesting results specific to human tissues were obtained with glutamate; succinate, fumarate, malate, and citrate were inactive, though nearly all increase respiration in absence of pulses.

In absence of any added oxidizable substrate human cerebral cortex respired at rates initially one-half or two-thirds of those with adequate glucose, but rates fell further after some 30 minutes. At no time was the rate in absence of substrate increased by applied pulses. It was decided to examine whether, in a series of experiments with varying glucose concentrations, metabolic changes could be seen in the separated tissue at glucose levels approximating those at which hypoglycemic symptoms become evident in vivo. This was not found to be the case with the unstimulated tissue, for glucose could be lowered from its normal 0.55 mM. to 0.05 mM. with extremely little change in respiration.[21] In vivo, cerebral respiration has fallen considerably at these levels of glucose.[22] However, applied pulses again rendered the separated tissue more akin to the tissue in vivo, for its response to pulses in vitro was reduced at glucose levels below 0.2 to 0.3 mM.

Survival Without Substrate.—In vivo, the effects of prolonged hypoglycemic coma have shown that glucose is necessary not only for immediate cerebral activities, but also for cerebral maintenance, because glucose lack for more than an hour or so may lead to permanent cerebral damage or to irreversible coma.* Comparable phenomena have now been found in the separated tissue by using the response to

¶ References 8, 9, and 13.

References 8 and 9.

* References 23 and 24.

pulses as a measure of functional integrity. Tissues were shaken in a saline complete except for glucose, and glucose was added to them after varying periods. After further periods, pulses normally effective were applied and the respiratory response noted.

It was found that not only did the respiratory rate fall in the absence of glucose, but also, on adding glucose after periods of 30 minutes or more at 37 C., normal rates were not recovered. This occurred both in gray and in white matter (Table 2). Respiratory response to applied pulses declined to an even greater extent than did the unstimulated respiration. Thus, response reached negligible proportions after two hours without glucose, though unstimulated respiration at that time was still 50 to 70% of that of tissue which had throughout been maintained in glucose. Thus, tissue lacking substrate is slowly failing; nevertheless, its maintenance for an hour or so at 37 C., in a condition later capable of responding, is an active process. This

TABLE 2.—*Survival of Response to Applied Pulses*

Experiment	Specimen	Time at 37 C. Without Glucose (Min.)	Respiratory Rate with Glucose (μmoles O_2/Gm./Hr.)	
			In 30 Min. Before Pulses Applied	During Pulses
A	Gray matter from cerebral cortex, frontal region	0	54	92
		45	40	78
		120	32	36
B	Subcortical white matter from frontal region	0	23	35
		45	13	29
		120	12	14

		Respiratory Rates (μmole O_2/Gm./Hr.)		
		First 30 Min.; Pulses and No Glucose	Second 30 Min.; No Pulses	Third 30 Min.; with Pulses
C	Gray; no addition in 2d period	56	40	31
	Gray; glucose added in 2d period	54	42	37
	Gray; glucose and fumarate added in 2d period	54	53	60

Specimens from three subjects were examined as slice fragments in phosphate salines in vessels with concentric electrodes 11 mm. apart. In A and B some vessels contained glucose throughout; in the others glucose was added at the times indicated. Respiration was measured for 30 minutes after addition of glucose, and again for the subsequent 30 minutes during application of condenser pulses of 0.4-msec. duration, and 18 volts peak potential at 100 per second. In C all tissues were first exposed to the pulses of the same characteristics for 30 minutes in absence of glucose. After the additions noted, the tissues metabolized for 30 minutes without and 30 minutes with pulses, again of the same type.

was shown by keeping the tissue in nitrogen rather than in oxygen. Its ability to respond later to pulses in the presence of glucose fell considerably in periods of less than 30 minutes rather than of 2 hours. The tissue maintained aerobically respired and formed CO_2 from endogenous substrates and this presumably aided its maintenance.

Pulses applied aerobically to tissue lacking substrate produced, as noted above, no immediate effect on respiration. Nor in tissues from experimental animals did they change other metabolic characteristics.[25] Nevertheless, they were found to have altered the tissue in a fashion which did not occur if they were applied in the presence of glucose, for their application in absence of substrate accelerated loss of excitability (Table 2). When glucose was subsequently added, respiratory response was greatly reduced in 30 minutes rather than in 2 hours.

Recovery of Response.—One interest in studying the failing tissue is the opportunity given to attempt to restore its normal response. In tissues from laboratory

animals, it had been noted [25] that when respiratory response to pulses was lost, glycolytic response remained. The tissue might thus have maintained the structural integrity needed for response but be lacking a metabolic step concerned in respiration rather than glycolysis. Other explanations are possible, but that suggested contributes to the failure, as was shown by supplying possible respiratory catalysts. After the tissue had respired without glucose but with applied pulses for 30 minutes, there was added not only glucose, but also, in different experiments, a wide variety of other substances. Of these, only two—fumaric and malic acids—were found to restore respiratory response. This result has been reproduced in human tissues (Table 2, Experiment C), though the specificity of fumaric acid in doing this has not been examined in this case. Only part of the normal response was recovered.

COMMENT

The organization of cerebral tissues appears to involve characteristics which make their metabolic response a more immediate measure of activity than is the case with peripheral nerve. Whereas increased respiration in amphibian peripheral nerve persists 15 minutes or more after stimulation,† the increase probably does not last 15 seconds in mammalian cerebral tissues.[16] Sympathetic ganglia are intermediate in this respect, the corresponding value being about four minutes.[28] Presumably, the closeness of linkage between activity and supporting metabolism contributes to making the brain the most sensitive organ to hypoglycemia or to anoxia. It also contributes to the success of the present experimental arrangements.

It is probable that the pulses which change the metabolism of separated cerebral tissues depolarize neuronal elements, and that the increase in energy-yielding processes which is measured is associated with subsequent repolarization.[29] Judged simply as a means of measuring response, and in comparison with electrical measurement of response in peripheral nerve, the present methods may seem relatively indirect and cumbersome. However, it appears certain that—again in distinction to observations in peripheral nerve—metabolic conditions in the case of mammalian cerebral tissues must be more carefully controlled before any measure of response can be obtained. The methods discussed above maintain satisfactory metabolic conditions and at the same time give opportunity of measuring both unstimulated and stimulated metabolic activities. From a biochemical point of view, they give a measure not only of the normal activities of the tissue, but also of the extent to which potential activities are limited or controlled. As is indicated above, abnormalities in such potential activities or their control may thus be revealed.

SUMMARY

Values are quoted for respiratory and glycolytic rates in human cerebral tissues examined under normal in vitro conditions and also during the application of fluctuating electrical potential gradients, which increased the metabolic rates.

The respiratory rates of the more normal tissues with applied pulses approximated those normal to the brain in vivo. The electrical characteristics required in pulses for metabolic effects were similar to those required for response in vivo from the exposed cerebral cortex.

† References 26 and 27.

In other tissues, application of pulses revealed metabolic abnormalities otherwise unapparent.

Similarities are noted between the response of tissues with applied pulses and those in vivo with respect to effects of absence of substrate and to the presence of substrates alternative to glucose.

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CLOT RETRACTION TIME AS A DIAGNOSTIC AID IN NEUROLOGY

J. PHILIP SAVITSKY, M.D.
CINCINNATI
AND
ROBERT WERMAN, M.D.
NEW YORK

AN INCREASED adhesiveness of the platelets has been observed in a number of physiological and pathological conditions.* Common to almost all these various conditions is an abnormally rapid growth of tissue occurring at any place in the body.[4] This is particularly well demonstrated by the presence of an elevated platelet adhesiveness in the postoperative period,† in the presence of both benign and malignant neoplasms,‡ and during a reticulocyte response to antianemic therapy.[4] An elevated platelet adhesiveness has been found associated with active multiple sclerosis, brain and spinal cord tumors, and the Guillain-Barré syndrome.[5] In the same study a normal platelet adhesiveness was found in infections, in vascular accidents, including thromboembolic phenomena, and in degenerative diseases of the nervous system.

The platelet adhesiveness has been shown to be closely correlated with the rate of initiation of clot retraction as measured by the clot retraction time.[6] An elevated platelet adhesiveness has been demonstrated to be always associated with an abnormally rapid clot retraction time. Within the normal range of number of circulating platelets, the platelet adhesiveness and clot retraction time were independent of the platelet count. A factor in the plasma, external to the platelets, has been demonstrated to be responsible for both the elevated platelet adhesiveness and the accelerated clot retraction time.[7]

The present investigation is a study of changes in the clot retraction time in various acute and chronic neurological conditions. These changes were found to parallel closely those previously reported for changes in the platelet adhesiveness. The clot retraction time was then evaluated for its possible use as an aid in diagnosis of central nervous system neoplasms.

EXPERIMENTAL STUDY

Methods of Determining Clot Retraction Time.—The clot retraction time was determined by the previously described method[6] of depositing a drop of recalcified venous blood in castor oil. In that procedure 1.8 ml. of venous blood was drawn into a syringe containing 0.2 ml. of

From the Division of Neuropsychiatry, Montefiore Hospital.
Aided by funds from the National Multiple Sclerosis Society.
Present Address: May Institute for Medical Research, Cincinnati (Dr. Savitsky).
* References 1 through 3.
† References 1, 2, and 4.
‡ References 2 and 5.

3.8% sodium citrate. The blood was placed in a glass tube and permitted to stand at room temperature for 10 minutes. One-tenth milliliter of a 5% $CaCl_2 \cdot 2H_2O$ solution was added, and the blood clotted in three to five minutes. Before clotting took place, two minutes after the calcium was added, blood was drawn up in a hemoglobin pipette and deposited as a single drop in castor oil. (Siliconized capillary pipettes which delivered 60 to 80 drops of water per milliliter were also used.) The tubes of castor oil were kept at 21 C. The test was done in triplicate. The tubes were observed, and the clot retraction time was taken as the time from the clotting of the recalcified blood in the tube to the exudation of serum from the drop in the castor oil. The mean value of the three determinations, if they were within five minutes of each other, was used. The normal range, as previously determined on 50 normal adults, was from 25 to 40 minutes, with a mean value of 32.1 minutes.[6] A clot retraction time of 22 minutes or less was considered abnormally rapid. The majority of rapid clot retraction times were between 15 and 20 minutes, a finding which corresponds to a platelet adhesive index range of 1.35 to 1.70.

Material.—Two hundred fifty hospitalized patients with neurological diseases were studied. The nature of the diseases and the number of cases of each are indicated in the Table. All cases of brain and spinal cord tumors were confirmed at autopsy or at operation. All cases considered to be cerebrovascular accidents had a history of sudden onset and gradual recovery,

Clot Retraction Time in Two Hundred Fifty Neurological Cases

Disorder	No. of Cases	Normal Clot Retraction Time	Abnormal Clot Retraction Time
Brain and spinal cord tumors	60	6	54
Cerebrovascular accidents	62	56	6
Degenerative diseases	56	54	2
Central nervous system infections	18	16	2
Chronic encephalitic Parkinsonism	4	0	4
Multiple sclerosis	50	..	..
1. Stationary	21	18	3
2. Fluctuating	26	5	21
3. Exacerbations	3	0	3

as observed over a period of several months. Most of the patients with cerebrovascular accidents had arterial hypertension or diabetes mellitus, and many had had diagnostic procedures, such as angiography or pneumoencephalography, performed. The patients with degenerative diseases had been in the hospital for long periods of time with the classical signs and symptoms and slow progression characteristic of such conditions as Parkinsonism, syringomyelia, amyotrophic lateral sclerosis, presenile dementia, Huntington's chorea, muscular dystrophy, and Friedreich's ataxia.

The 50 patients with multiple sclerosis were divided into three groups, as in a previous study.[5] Patients whose disease was considered stationary were those who had had no new symptoms or signs for at least six months preceding the investigation. The group with fluctuating multiple sclerosis consisted of patients who reported frequent new symptoms or fluctuations of old symptoms that often could not be corroborated by neurological examination. The patients in acute exacerbation were those who complained of the rapid development of new symptoms and had clinically verifiable objective signs which had not been present previously.

RESULTS

Clot retraction time determinations were performed in 250 cases with a variety of diagnoses from the neurological and medical services of Montefiore Hospital. Repeated determinations were done in many cases during the course of their illness. A summary of the results is found in the accompanying Table. Ninety per cent of the patients with neoplasms of the central nervous system had an abnormally rapid

clot retraction time. This includes cases of metastatic malignant tumors, gliomas, pituitary adenomas, meningiomas, and acoustic neuromas. Of the six tumors associated with a normal clot retraction time, three were meningiomas with histories of neurological symptoms dating back 10 years or more. Another tumor associated with a normal clot retraction time was a pituitary adenoma which had been treated successfully with radiation.

About 10% of the patients with cerebrovascular accidents, degenerative diseases, and central nervous system infections had a rapid clot retraction time. Four cases of chronic encephalitic Parkinsonism had a consistently abnormal retraction time on repeated determinations. The results of the studies of the multiple sclerosis patients were similar to those previously reported for changes in the platelet adhesiveness in multiple sclerosis.[5] Of the 21 patients tested whose disease was considered stationary, only 3 had abnormally rapid clot retraction times. However, 21 of the 26 fluctuating cases had abnormal retraction times, and all 3 of the cases in acute exacerbation had a rapid retraction time.

These data suggested the use of the clot retraction time as an aid in the diagnosis of brain and spinal cord tumors, since 90% of the neoplasms were associated with an abnormally rapid clot retraction time and only about 10% of the other neurological disorders (excluding multiple sclerosis) had abnormal retraction times. Forty-five cases admitted to the hospital as "brain tumor suspects" or "spinal cord tumor suspects" had their clot retraction times determined on admission before any diagnostic work-up was done. These 45 cases are selected from a larger group of over 100 similar cases which were tested on admission to the hospital, because in all these 45 cases a definitive diagnosis was reached by autopsy, operation, pneumoencephalogram, ventriculogram, angiogram, spinal fluid changes, or later course of the disease. Only three of the patients were under the age of 40. An abnormally rapid retraction time was considered evidence of either a tumor or multiple sclerosis (in the younger patients), and a normal retraction time, as evidence of other neurological disease. In 40 of these 45 cases the clot retraction time accurately predicted the presence or absence of a tumor. Two of the patients under the age of 40 with an abnormal retraction time were demonstrated to have active multiple sclerosis. Three of the five cases in which the test was in error had huge, slowly growing meningiomas, with neurological histories going back 10 years or more. Most of the cases had many repeated determinations performed, and it was observed that the test became unreliable after procedures such as angiography and pneumoencephalography and during infections and periods of elevated body temperature.[4]

COMMENT

The evidence presented here shows that there is an abnormally rapid clot retraction time associated with central nervous system neoplasms and with multiple sclerosis. Other neurological conditions had consistently normal retraction times. In a series of 45 patients admitted to the hospital as brain or spinal cord "tumor suspects," the clot retraction time was correct in predicting the presence or absence of a tumor in 40.

Increased platelet adhesiveness has been correlated by some investigators with a predisposition to thromboembolic phenomena and vascular disease.§ This correla-

§ References 1 and 2.

tion has not been confirmed by Eisen and associates,[3] or by us in another study.[4] In a large series it was found that cases of myocardial infarctions, thromboembolic episodes in the extremities, diabetes mellitus, and arterial hypertension had a consistently normal platelet adhesiveness and clot retraction time. Moreover, many conditions with elevated adhesiveness and rapid retraction time, such as neoplasms, skin disease, liver cirrhosis, leukemia, anemias responding to therapy, and the Guillain-Barré syndrome, are not associated in any way with thromboembolic disorders. The conclusion, therefore, is that an increased platelet adhesiveness and a rapid clot retraction time are not associated with thromboembolic phenomena and do not indicate pathological changes in the blood-clotting mechanism as far as is known at present.

An abnormally rapid clot retraction time and an elevated platelet adhesiveness are associated with abnormally rapid growth of tissue. In all forms of neoplastic disease, both benign and malignant, there is an abnormal clot retraction time. The changes observed in this study of neoplasms of the nervous system represent a nonspecific effect produced by all rapidly growing tumors. It is interesting to note that three tumor cases in which there was a normal retraction time were those of slowly growing meningiomas with long neurological histories.

Although these studies were thought initially to support the theory of venule thrombosis in multiple sclerosis,[5] the lack of relation of thromboembolism to changes in the platelet adhesiveness and clot retraction time indicates that these data are not evidence for the thrombotic etiology of multiple sclerosis. Rather, an elevated platelet adhesiveness and a short clot retraction time in active multiple sclerosis suggest that some growth process is taking place during the periods of fluctuation and acute exacerbation. The consistent normal values found in vascular accidents and inflammatory processes speak against these factors as pathogenetic in multiple sclerosis. The platelet adhesiveness and clot retraction time have been shown to be entirely normal in such allergic disorders as bronchial asthma and in conditions related to hypersensitivity, such as acute rheumatic fever and glomerulonephritis.[4]

The clot retraction time has been found to be valuable clinically in differentiating nervous system neoplasms from vascular, degenerative, and infectious diseases. An abnormal retraction time in a tumor suspect has been found in this study to be associated with a neoplasm in 90% of the cases. In persons under the age of 40, multiple sclerosis was commonly associated with an accelerated retraction time, so that it cannot be differentiated from a neoplasm on the basis of this test. A normal retraction time in a tumor suspect indicated some other neurological disease in 90% of the patients. A positive test (rapid retraction time) was of particular value in cases in which a neoplasm was not seriously considered because it suggested that a more intensive search for a tumor was warranted. The limitations of the clot retraction time as an aid in neurological diagnosis are its nonspecificity for the nervous system and its variability following procedures and in acute infections. For one to three days following pneumonencephalography or angiography there is a moderate acceleration of clot retraction. During infections and periods of elevated body temperature there appears to be an inhibition of the clot retraction time, so that normal values will be found even in the presence of a rapidly growing malignant neoplasm.[4]

SUMMARY AND CONCLUSIONS

The rate of initiation of clot retraction as measured by the clot retraction time was studied in 250 neurological cases. An abnormally rapid clot retraction time was observed to be associated with neoplasms of the nervous system and with fluctuating multiple sclerosis. This test was found to be valuable as an aid in the diagnosis of nervous system neoplasms and as an indicator of activity in multiple sclerosis.

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THREE-YEAR FOLLOW-UP OF PATIENTS DEVELOPING EOSINOPHILIA DURING INSULIN COMA THERAPY

R. V. FREEMAN, M.D.
T. E. JONES, M.D.
AND
J. J. PALMER, M.D.
LOS ANGELES

RECENT studies have suggested that the development of blood eosinophilia during insulin coma therapy may have prognostic significance.[1] These observations have for the most part been concerned with the immediate clinical response to insulin coma therapy. In order to evaluate the continued benefit of therapy, we have done a three-year follow-up study of 11 patients whose blood eosinophile levels were recorded as part of a pilot study of various metabolic changes in a consecutive series of patients receiving insulin coma therapy at our hospital between January and September, 1950. Changes in blood cholesterol and blood cholesterol esters have been reported elsewhere by Goodman and Kanter.[2]

METHODS

In our hospital patients are selected for insulin coma therapy by a medical board consisting of the chief, acute-intensive treatment service; the ward physician, and the resident in psychiatry. Prior to presentation the patients have a thorough work-up, which includes psychiatric evaluation, medical consultation, psychologic battery, and social service evaluation. Routine laboratory examinations include electroencephalography, electrocardiography, complete blood cell counts, blood eosinophile counts, urinalysis, blood serology, and stool examination for parasites. In general, the patients selected were young, had an active paranoid psychosis, and were free of acute behavior disturbance. Routine laboratory examinations were negative in the 11 patients of this study.

The patients received insulin coma therapy according to the technique recommended by Bond and Shurley.[3] Treatments were given five days a week, with weekend rest, until an average total of 32 comas was reached. On treatment days fasting patients received intramuscular injections of insulin at 7:00 a. m. The initial dose in all cases was 20 units, and thereafter the dose was doubled each successive day until the patient entered coma at 9:00 a. m. However, if coma did not result from the administration of as much as 1,000 units of insulin, the dose was then decreased to the neighborhood of 250 to 500 units, and this lower dose was continued until coma occurred. In all instances the desired result was the onset of coma two hours after injection, and whenever possible a short period of deep midbrain coma was attained at approximately 9:30 a. m. Termination of midbrain coma was accomplished by

From the Veterans Administration Center, Los Angeles, and the Department of Pathology (Dr. Palmer), University of California School of Medicine at Los Angeles.

intravenous injection of dextrose. Less profound coma was terminated by gavage, reinforced with sweetened beverages when the patient had regained consciousness. In every instance in this series treatment was completed by 10:00 a. m.

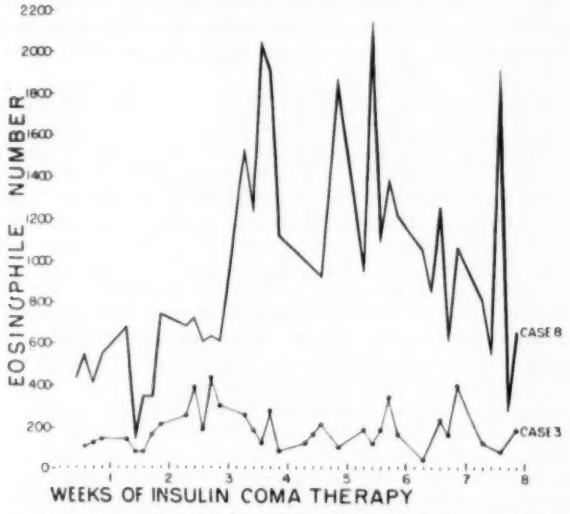
Eosinophile counts were done by Randolph's method,[4] the same technician performing all the counts during the entire study. Counts were made before, during, and after the course of insulin coma therapy. During therapy the counts were made at about 9:30 a. m., the usual time of deepest coma.

The clinical response to insulin coma therapy was evaluated in each case during therapy and again three years later. For the purpose of our study, "response" was defined in two categories, "improved" and "unimproved." The factors of behavioral improvement, symptomatic improvement, and the levels of social and occupational adjustment after discharge were considered. The weight of any single factor in the total evaluation depended on the clinical picture. For example, a patient remaining on an open ward of the hospital for the full period of three years might well be much improved as compared with his pre-insulin-coma-therapy state; a patient making a precarious adjustment outside the hospital after three years might well be worse or unimproved as compared with his pre-insulin-coma-therapy state. Of the 11 patients, 5 now in our hospital were personally examined by one of us. Of the six patients discharged from the hospital, three are now residing in Southern California, one left the United States on board a merchant ship in July, 1951, one is visiting relatives in Greece, and one is supporting his family in Florida. These six patients were evaluated from the clinical records and special social service investigation, with emphasis on the presence or absence of symptoms, and on social, familial, and occupational adjustment.

OBSERVATIONS

Eosinophile Response.—Eosinophile counts on 10 patients prior to insulin coma therapy and on 8 patients after insulin coma therapy failed to show significant variation beyond the normal ranges given by Rud,[5] Best and Samter,[6] and Fisher and Fisher.[7] This study relates to a total of 373 eosinophile counts done on 11 patients at times of deepest coma during insulin coma therapy. Inspection of individual records revealed that some patients developed eosinophilia and others did not. For example, Case 8 (Chart) developed eosinophilia, with a maximum number of 2,134 eosinophiles per cubic millimeter during the sixth week, while Case 3 showed minimal eosinophile response, with a maximum number of 440 per cubic millimeter during the third week of therapy. Further inspection of the 373 eosinophile counts, divided into eight periods corresponding to the successive weekly periods of insulin coma therapy, revealed that there was a total of four cases showing minimal eosinophile response, similar to that in Case 3. Statistical analysis revealed that the 11 patients could be divided into two groups on the basis of significant differences in eosinophile response. As shown in the Table, the difference in response first became statistically apparent during the fourth weekly period of insulin coma therapy, when the mean value of 16 counts in Series I was 240 per cubic millimeter and the mean value of 32 counts in Series II was 870 per cubic millimeter. This difference persisted throughout the remaining weekly periods of therapy, being most prominent during the sixth weekly period. During the sixth weekly period of insulin coma therapy, the mean value of 19 counts in Series I was 350 per cubic millimeter, and the mean value of 35 counts in Series II was 1,310 per cubic milli-

meter. In the statistical analysis, a range of 3 σ about each mean value encompassed approximately 99% of the individual counts on which the mean was based, and beginning with the fourth weekly period of insulin coma therapy there was no overlapping in the standard deviation of distribution of the mean values of Series I and Series II.



Variation in eosinophile numbers at time of deepest coma during weekly periods of insulin coma therapy. Case 3 shows minimal eosinophile response and Case 8 shows eosinophilia.

*Number of Counts, Mean and Standard Deviation of Mean of Daily Direct Eosinophile Counts of Four Patients Who Showed Minimal Eosinophile Response and Seven Who Developed Eosinophilia During Eight Weeks of Insulin Coma Therapy**

	Series I: Four Patients Showing Minimal Eosinophile Response			Series II: Seven Patients Showing Eosinophilia		
Week of Therapy	No. of Counts	Mean Weekly Count	Standard Deviation of Distribution	No. of Counts	Mean Weekly Count	Standard Deviation of Distribution
1	15	130 ± 17	66	24	210 ± 34	165
2	20	250 ± 36	163	30	320 ± 49	270
3	16	350 ± 34	136	33	540 ± 48	274
4	16	240 ± 20	82	32	870 ± 89	503
5	19	310 ± 29	128	27	900 ± 110	572
6	19	350 ± 32	138	35	1,310 ± 88	520
7	18	340 ± 37	157	31	1,040 ± 74	411
8	10	240 ± 34	107	28	1,050 ± 104	550

* Counts were done at time of deepest coma.

Clinical Response.—Series I: The clinical course of the four patients in this series, showing minimal eosinophilia response during deepest coma in insulin coma therapy, has been as follows:

CASE 1.—R. A., a single white man, age 38. The onset was in 1945, with alcoholism and visual and auditory hallucinations. He had had severe persecutory delusions and combative behavior since 1948. There were suicidal attempts. He had insulin coma therapy from June 14 to Aug. 4, 1950, with 31 comas, and total insulin 11,330 units. The mean of five eosinophile

counts during the sixth weekly period was 480 per cubic millimeter. During treatment he remained quiet, suspicious, and hostile. During the follow-up period he had many episodes of unauthorized absence, with heavy drinking and repeated discharges against medical advice. In June, 1951, trial visit in custody of his mother failed because of alcoholism, ideas of reference, depression, agitation, and seclusiveness. After an erratic course in the hospital, trial visit with his mother was again attempted in May, 1952. A social service report of August, 1953, reveals a very dubious state of affairs according to the mother and sister. While he is now somewhat less combative, he has been totally unemployable and episodes of drinking have become much more frequent, so that periods of sobriety are not longer than one week, whereas formerly he might stay sober as long as a month.

Psychiatric Evaluation.—Unimproved during therapy and unimproved after three years.

Case 2.—M. W. L., a single white man, age 38. The onset was in 1942, in the Army, with bizarre behavior and delusions of persecution. He was discharged in May, 1943. He was transferred here from a state hospital, where he had been committed for belligerent and combative behavior. He had insulin coma therapy from June 14 to Aug. 14, 1950, with 38 comas and total insulin, 10,430 units. The mean of five eosinophile counts during the sixth weekly period was 416 per cubic millimeter. During treatment he showed some reduction in acute symptoms. During the follow-up period he remained hostile and paranoid, especially toward the Veterans Administration. In November, 1950, he was placed on trial visit in the custody of his father. It was reported that the community received him tolerantly, accepting his peculiar and unusual behavior, so that he was able to avoid overt difficulties. He remained unemployable, largely because of his suspicious and hostile manner. Although his outside adjustment was precarious, he was discharged from trial visit when one year was completed. Thereafter, he made and broke a number of appointments with the social worker in his area. He finally arrived on one occasion, spending the entire interview in a tirade against his wife and the Veterans Administration. His manner was hostile, belligerent, and confused. Current social service investigation reveals that he disappeared from home about two years ago, and his relatives have not heard from him since. Inquiries in various cities where he might have wandered have not been successful.

Psychiatric Evaluation.—Improved during therapy and unimproved after three years.

Case 3.—E. M. H., a single white man, age 26. The onset was in March, 1950, with confusion, emotional flattening, and many bizarre delusions. He had insulin coma therapy from July 5 to Aug. 29, 1950, with 33 comas, and total insulin 11,260 units. The mean of five eosinophile counts during the sixth weekly period was 211 per cubic millimeter. During treatment he was resistive and uncooperative. During the follow-up period the delusions were unchanged, and he remained resistive and negativistic. Early in 1951 he became very hyperactive and assaultive, but after a course of 40 electronarcosis treatments there was some reduction in gross behavior disturbance. He has remained in the ward for disturbed patients ever since. Currently he is withdrawn and asocial and constantly responds to hallucinations. There has been no response to motivation therapy. He becomes hostile when contact is attempted.

Psychiatric Evaluation.—Unimproved during therapy and unimproved after three years.

Case 4.—R. C. J., a single white man, age 30. The onset was in 1945 with bizarre somatic complaints. He received a medical discharge from the service in 1946 for conversion reaction. He was admitted here in 1950 as presenting an unclassified schizophrenic reaction, and his somatic delusional system proved to be unshakable. He had insulin coma therapy from May 15 to June 30, 1950, with 25 comas, and total insulin 6,250 units. The mean of 5 eosinophile counts during the sixth weekly period was 258 per cubic millimeter. During therapy no change was observed, and in December, 1950, he was discharged, against medical advice. During the follow-up period he remained at home with his mother and had no social contacts or friends. He had some very brief periods of ineffective employment, and there were repeated periods of clinic or hospital attention for a variety of genitourinary and gastrointestinal complaints. In August, 1953, he was readmitted for continued psychiatric care. Currently, there is progression of the psychotic reaction. Affectivity is flat, and he speaks only in mumbled phrases, with content concerned as before with somatic complaints, primarily referred to the rectum and bladder. Insight is nil, and he remains hostile and negativistic.

Psychiatric Evaluation.—Unimproved during therapy and unimproved after three years.

Summary of Eosinophile and Clinical Response Patterns in Series I.—In general, the four patients in this series were young, were hospitalized because of an active paranoid psychosis requiring psychiatric nursing care, and were sufficiently free of acute behavior disorder as to be able to cooperate during the course of insulin coma therapy. Their ages varied from 26 to 38 years, with an average age of 33 years. The duration of symptoms prior to insulin coma therapy varied from four months to eight years, with an average of four years. All had military service during World War II. The number of deep comas attained during insulin coma therapy varied from 25 to 38, with an average of 31. The total amount of insulin administered during a course of insulin coma therapy varied from 6,250 to 11,330 units, with an average of 9,817 units. The mean values of eosinophile counts during time of deep coma in the sixth weekly period of therapy varied from 211 to 480 per cubic millimeter, with an over-all mean value of 350 per cubic millimeter. The clinical responses to insulin coma therapy were consistently disappointing, as only one patient showed perceptible improvement during therapy and none of the four patients was improved three years later.

Series II: The clinical course of the seven patients in this series, showing definite eosinophilia during deepest coma in insulin coma therapy, has been as follows.

CASE 5.—S. C., a divorced white man, age 31. The onset was in 1946. He had had constant neuropsychiatric care since discharge from the military service. On admission here in December, 1949, he showed marked affective flattening, persecutory delusions referable to the Veterans Administration, and an outstanding set of grandiose delusions. He had insulin coma therapy from Jan. 10 to March 3, 1950, with 34 comas, and total insulin 10,590 units. The mean of five eosinophile counts during the sixth weekly period was 1,320 per cubic millimeter. During therapy no significant improvement was noted, and a few months later the patient had a full course of electroconvulsive therapy. In August, 1951, trial visit was unsuccessful because of his hyperactivity and confusion. His paranoid delusional system was associated with considerable behavior disturbance, and a prefrontal lobotomy was done in March, 1953. Currently, his acute behavior disturbances have cleared up, but he remains manneristic, preoccupied, and delusional. Although he is cooperative on the continued-treatment ward, he refuses most activities other than routine care and recreations.

Psychiatric Evaluation.—Unimproved during therapy and unimproved after three years.

CASE 6.—D. M., a separated white man, age 37. The onset was in 1948, when he manifested bizarre behavior and alcoholism. He was committed and admitted in March, 1949. Admission examination disclosed auditory hallucinations and many poorly organized paranoid delusions. He was demanding, hyperactive, and combative. He had insulin coma therapy from June 5, 1950, to July 26, 1953, with 33 comas, and total insulin 8,290 units. The mean of five eosinophile counts during the sixth weekly period was 986 per cubic millimeter. During therapy he became cooperative and amiable. During the follow-up period the administrative improvement persisted, but there was a return of some demanding behavior and delusional paranoid ideas. A course of electronarcosis late in 1950 seemed to have no effect. In September, 1951, trial visit was unsuccessful because of increased psychomotor activity at home. Thereafter his conduct on the preprivilege ward was satisfactory, except for occasional unauthorized absences from the hospital. Currently, he is usually quiet, though sometimes demanding. He is well nourished and neat. His manner varies from alertness to seclusiveness. There is blocking and flight of ideas. He remains delusional and claims that his hospital discharge should be based on his American citizenship.

Psychiatric Evaluation.—Improved during therapy and unimproved after three years.

CASE 7.—D. O. B., a divorced white man, age 33. The onset was in 1943. Since discharge from the military service he has had numerous admissions to neuropsychiatric hospitals. He was last admitted here in April, 1950, because of severe behavior disturbances related to an extensive delusional system—persecutory, grandiose, and somatic. He had insulin coma therapy

from July 5 to Aug. 29, 1950, with 37 comas, and total insulin 23,330 units. The mean of five eosinophile counts during the sixth weekly period was 1,384 per cubic millimeter. During therapy there was some symptomatic improvement. During the follow-up period his clinical course has been erratic. His preoccupation with his role in a giant dope ring and the F. B. I. has been less, but closed-ward care has been required because he would become intoxicated during unauthorized absences from the hospital. Currently, there is little evidence of his paranoid delusional system, but a high degree of security is necessary because of the continued tendency to elope and become involved in conduct disturbances when away from the hospital.

Psychiatric Evaluation.—Unimproved during therapy and unimproved after three years.

CASE 8.—A. V. D., a single white man, age 29. The onset was in 1946. He was admitted in October, 1949, in a near-panic state, with severe tension, anxiety, and a variety of bizarre somatic complaints. During intensive psychotherapy no diminution of symptoms was noted. He had insulin coma therapy from May 2 to June 23, 1950, with 31 comas, and total insulin 13,830 units. The mean of five eosinophile counts during the sixth weekly period was 1,359 per cubic millimeter. During therapy the acute symptoms abated. During the follow-up period the patient received unusual benefit from individual and group psychotherapy, receiving a maximum hospital benefit discharge in December, 1950. Since then he has lived with his parents and has continued psychotherapy on a private basis. He has been employed most of the time but has had various jobs. According to social service investigation in July, 1953, there is some friction in the family, but the veteran is able to handle this without undue anxiety. He seems to enjoy several sports, and he dates with some regularity. Currently, he is employed as a title searcher in an insurance company. He likes this work and is apparently performing well.

Psychiatric Evaluation.—Improved during therapy and improved after three years.

CASE 9.—A. S. C., a single white man, age 36. The onset was in 1945. There have been several neuropsychiatric admissions since his discharge from military service, following several years as a prisoner of war in Japan. His last admission was in December, 1949, after five months outside the hospital. He was tense, fearful, and expressed severe phobias related to venereal disease and entering any men's toilet. He had insulin coma therapy from Jan. 10 to March 9, 1950, with 33 comas, and total insulin 11,180 units. The mean of five eosinophile counts during the sixth weekly period was 1,619 per cubic millimeter. During therapy he became more optimistic and the tension and fearfulness decreased, so that for the first time in some years he was able to make a few friends. During the follow-up period he made his own plans for outside living and employment and was discharged with maximum hospital benefit in April, 1950. Thereafter he lived alone in a nearby community and maintained some limited social contact with the Y. M. C. A. His physical state remained improved, and he kept some increased weight. There was no recurrence of his previous bizarre social patterns. He has relied on his pension checks for most of his support. For the past several months he has been visiting relatives overseas. It does not seem that he has required or sought medical care since the time of his discharge.

Psychiatric Evaluation.—Improved during therapy and improved after three years.

CASE 10.—R. W., a married white man, age 32. The onset was in 1944. He received a medical discharge from the military service for a service-connected psychiatric disorder. Voluntary admission here was in April, 1950, because of nervous tension and ideas of reference, with poor social adjustment due to incapacitating withdrawal and seclusiveness. Admission examination revealed ideas of reference, auditory hallucinations, and paranoid delusions. He had insulin coma therapy from May 10 to July 10, 1950, with 30 comas, and total insulin 11,560 units. The mean of four eosinophile counts during the sixth weekly period was 1,714 per cubic millimeter. During therapy there was a gradual remission of symptoms, and by the end of the course he was much more sociable and demonstrated fairly normal affect. During the follow-up period on an open ward he was free of symptoms and adjusted well. He was able to make adequate plans for outside living and was discharged with maximum hospital benefit in October, 1950. Social service investigation in October, 1953, described a very good adjustment at home with his family in Florida. He is steadily employed, and recently his service-connected pension was reduced. Community sources reveal that he has fitted in well, and his relationships with supervisors and co-workers on the job have been good.

Psychiatric Evaluation.—Improved during therapy and improved three year later.

CASE 11.—S. H. T., a divorced white man, age 36. There was onset of a schizophrenic reaction five months before his admission to the neuropsychiatric hospital in June, 1950. While here, physical examination revealed evidence of Hodgkin's disease, a diagnosis which was verified by biopsy, and he received x-ray therapy. He had insulin coma therapy from July 5 to Aug. 25, 1950, with 30 comas, and total insulin 12,690 units. The mean of five eosinophile counts during the sixth weekly period was 772 per cubic millimeter. During therapy there was improvement in the psychosis. During the follow-up period plans for outside living were retarded because of an involved and fluctuating course of marital strife. Finally, he was placed on trial visit in May, 1951, and continued to receive psychotherapy at the mental hygiene clinic. He was reported to be free of symptoms at the time of his discharge from trial visit in May, 1952. According to social service investigation in July, 1953, he has adjusted well in the face of rejection by his wife and other family difficulties. Currently, he lives by himself and augments his pension by part-time work. Recently, he was able to buy a car. The current picture seems best interpreted as semi-independent community living, maintained with some effort.

Psychiatric Evaluation.—Improved during therapy and improved after three years.

Summary of Eosinophile and Clinical Response Patterns in Series II.—In general, the seven patients in this series were also young, were hospitalized because of an active paranoid psychosis requiring psychiatric nursing care, and were sufficiently free of acute behavior disorder as to be able to cooperate during a course of insulin coma therapy. In Case 11, Hodgkin's disease was an incidental finding during hospitalization. The ages of the seven patients varied from 29 to 37 years, with an average of 33 years. The duration of symptoms prior to insulin coma therapy varied from five months to seven years, with an average of four years. All had military service during World War II. The number of times deep coma was attained varied from 30 to 37, with an average of 33 comas. The total amount of insulin administered during a course of insulin coma therapy varied from 8,290 to 23,330 units, with an average of 13,067 units. The mean values of eosinophile counts during times of deep coma in the sixth weekly period of therapy varied from 772 to 1,714 per cubic millimeter, with an over-all mean value of 1,310 per cubic millimeter. The clinical responses to insulin coma therapy were variable, with a distribution in accordance with the usual experience in our hospital and as reported in the literature. Six of these seven patients showed perceptible improvement during insulin coma therapy, and four of the seven showed continued benefit of therapy after three years. There was no strict relationship between the degree of clinical improvement and various factors, such as the age of the patient, the duration of symptoms prior to insulin coma therapy, the number of times deep coma was attained, the amount of insulin required to produce coma, or the degree of eosinophilia recorded during insulin coma therapy. A notable exception to the coincidence of eosinophilia during insulin coma therapy and clinical improvement was Case 5, who developed a peak count of 1,760 per cubic millimeter but failed to show improvement during therapy, and whose subsequent course has been unremitting in spite of electroconvulsive therapy and a prefrontal lobotomy. The best clinical result was attained in Case 8, whose eosinophile response was about the same as that of Case 5. His peak eosinophile count was 2,134 per cubic millimeter, there was a striking abatement of acute symptoms during insulin coma therapy, and he is currently employed in a responsible position.

COMMENT

Alterations in the blood picture following the injection of insulin have been studied intensively since 1948, when Baird and Dixon [8] reported an extensive

investigation of 64 schizophrenic patients undergoing insulin coma therapy. They found that a large dose of regular insulin given to fasting patients invariably provoked a striking leucocytosis within one hour after its administration, with a peak between the third and fifth hour and a return to normal levels at 24 hours. The rise in the total white cell count was largely neutrophilic. Although a moderate lymphocytosis was apparent by the second hour, the levels fell to a lymphopenia by the sixth hour, with return to normal absolute numbers of lymphocytes by the ninth hour after injection of insulin. They noted the tendency of eosinophiles and basophiles to disappear between the third and fifth hour, when leucocytosis was at the peak. There was only a slight rise in red blood cells, hemoglobin, and hematocrit values, as shown in counts taken four hours after insulin administration. They found no general relationship between the degree of leucocytosis and the amount of insulin given, and the alterations in the blood picture were apparently as great after 40 days of treatment as during the first few days.

Since 1949, when the rapid direct method of counting eosinophiles became available, the attention of many investigators has been directed toward the relationship between changes in eosinophile levels and the response of the pituitary-adrenal system to various types of somatic stress, including insulin coma therapy. Some preliminary reports suggested that the absolute number of blood eosinophiles might be an index of the activity of the adrenal cortex. More recent reports, however, show that the mechanisms of regulation of blood eosinophile level are multiple and complex. Hoagland and associates [9] conclude that the eosinophile count is an unreliable measure of adrenal responsivity in man. The mechanisms regulating the eosinophile level during insulin coma therapy are obscure. Our observation of the transitory nature of eosinophilia during insulin coma therapy is in agreement with the reports of Alexander and Neander [1] and Shands and Menzer.[10] These authors found that in some patients, during a course of insulin coma therapy, there is a gradual increase in the eosinophile level from a normal range at the beginning of treatment to an average peak of about 600 per cubic millimeter at the 40th day of treatment. In these patients the eosinophile level then gradually falls and approaches the normal range by the time treatment is completed, at 70 days.

Alexander and Neander [1] suggest that changes in the eosinophile level during somatic stress, such as occur during electric shock therapy and insulin therapy, may give a clue to the patient's prognosis. Their conclusions are based on a total of 380 eosinophile counts done on 56 patients, approximately 7 counts per patient. These counts were done at intervals of about two weeks, before, during, and after electric shock therapy and/or insulin therapy. Twelve of these 56 patients failed to show eosinophilia, and all remained unimproved clinically. Forty-four of these 56 patients showed eosinophilia at the sixth weekly period of therapy, and 33 were "improved" or "much improved." In percentages, 75% of the patients with eosinophilia showed improvement in their mental condition. Shands and Menzer [10] followed the changes in 265 eosinophile counts on 27 patients during the course of insulin coma therapy. They found that these patients could be divided into two subgroups on the basis of the highest level of eosinophile count observed. In the smaller group, of 10 men, the highest eosinophile count observed was 303 per cubic millimeter, and 3 of these patients were classed as showing "excellent" immediate

clinical response. In the larger group, of 17 men, the highest count observed was in the 5,000 + level. In the larger group there were also three patients classed as showing "excellent" immediate clinical results. Some of the patients classed as showing "excellent" responses had relapses in a few months, and the authors feel that the evidence of prognostic significance of the occurrence or nonoccurrence of eosinophilia is not very convincing on the basis of their series. We followed the changes in 373 eosinophile counts on 11 patients during courses of insulin coma therapy. In the smaller group, of four men, showing minimal eosinophile response, only one showed perceptible improvement during treatment, and none was improved after three years. In the larger group, of seven men, six showed perceptible improvement during treatment and four showed continued benefit of therapy after three years.

Combining the observations of Alexander and Neander [1] and Shands and Menzer [10] with our own, we find a total of 1,018 eosinophile counts on a total of 94 patients. Of all the patients, 26 failed to manifest a significant degree of eosinophilia during therapy, and among these patients only 4, or 15%, showed immediate improvement. Such results as these are sufficiently at variance with the usual clinical experience as to warrant further investigation. On the basis of our pilot study, it appears that the time at which counts are done is critical. Eosinophilia is most prominent during the sixth weekly period after treatment is started, if present at all during the course of therapy. Eosinophile counts should be done at some particular time each day in every instance if the numbers are to be compared. Preferably, the counts should be done within two and one-half hours of the injection of insulin in order to be within the latent period of the daily drop in eosinophile level in response to stress. For example, if insulin is injected intramuscularly in fasting patients during the sixth weekly period at 7:00 a. m., the level of eosinophiles drops 50% or more between 9:30 and 11:45 a. m. As to the value of the eosinophile response as an aid in predicting the probability of prolonged remission of schizophrenia, our pilot study of 11 patients can only suggest that the eosinophile response, or perhaps some other, more reliable measure of somatic response to stress, may prove to be useful.

SUMMARY AND CONCLUSIONS

A three-year follow-up study was made of 11 patients, whose blood eosinophile levels were recorded as part of a pilot study of various metabolic changes in a consecutive series of patients receiving insulin coma therapy at our hospital between January and September, 1950. The patients were young male veterans of World War II, requiring psychiatric hospital care for an active paranoid psychosis. Statistical analysis of 373 eosinophile counts done on these 11 patients at the time of deep coma revealed that 7 patients developed definite eosinophilia, with the highest level during the sixth weekly period of insulin coma therapy. Six of these seven patients showed perceptible clinical improvement during therapy, but only four of the seven showed continued benefit of therapy after three years. A smaller group, of four patients, failed to manifest eosinophilia during the course of insulin coma therapy. Only one of these four patients showed perceptible clinical improvement during therapy, and none of the four was improved after three years.

Our pilot study suggests that further investigation of metabolic changes during insulin coma therapy is warranted, in order to determine the value of the blood

eosinophile level (or perhaps some other, more reliable measure of somatic adaptation to stress) as an aid in predicting the probability of prolonged remission of schizophrenia.

Dr. E. L. Lucia, Consultant in Biostatistics, prepared the statistical analysis of the data; Miss Barber Moyer, Medical Technician, performed the eosinophile counts, and Miss Dorthea Lane, Chief of Psychiatric Social Service, made special social service investigations.

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MULTIPLE SCLEROSIS IN TURKEY

Etiologic and Symptomatologic Study of Four Hundred Ten Cases

NUSRET MUTLU, M.D.
ANKARA, TURKEY

MULTIPLE sclerosis has been a subject of great importance and wide research in neurology during recent years. Much attention has been given to geographic and racial conditions, as well as to the etiologic, pathogenic, symptomatologic, and therapeutic study of the disease. I have studied multiple sclerosis in Turkey with consideration of the two former factors and, besides this, have compiled the etiologic and symptomatologic statistics on 410 cases that were collected from most of the larger hospitals.

The present medical publications indicate that multiple sclerosis exists in almost every country and no race is completely immune to it. Only in some geographic zones and among some races is there a striking difference in regard to the proportion of afflicted persons.

In the statistics which were made in Boston [1] and in Greater New York,[2] the incidence of multiple sclerosis for the white population was found to be about 4.3 to 6 in 10,000, and for the Negro population only 1.4 in 10,000. This proportion is lower in the countries of North and Middle Europe, such as Sweden,[3] Denmark,[4] Bohemia-Moravia,[5] and Switzerland,[6] than in the United States. On the other hand, cases of multiple sclerosis are rare in southern European countries, such as Italy, Spain, Rumania, and the Mediterranean coast of France.[7] It is seldom found in South Africa,[8] Brazil,[7] China,[9] Japan,* India,[11] or Netherlands East India.[12]

No wide study of multiple sclerosis in Turkey has been made to date. In 1934 Uzman and Aksel [13] studied this subject on the basis only of the materials of two hospitals from 1921 to 1934, and they came to the conclusion that the disease is seldom seen in Turkey and that it is found only among the people of the port towns and those who have visited Europe. In 1949 Gökay [14] reported on the symptomatologic study of 125 patients with multiple sclerosis who had been hospitalized between 1933 and 1949 at the neurological clinic of the medical school in Istanbul and noted the increase of cases in Turkey during the last two decades. In 1951, with Adasal I reported [15] the symptomatologic data on 168 cases that were observed between 1930 and 1950 at the Gülhane Military Medical Academy, coming to the same conclusion.

Read before at the Fourth Annual Session of the Gülhane Military Medical Academy, Jan. 24, 1953.

From the Department of Psychiatry of Ankara University (Prof. R. Adasal) and the Department of Neuro-Psychiatry of the Gülhane Military Medical Academy (Asst. Prof. S. Doğulu).

* Miura, K., in discussion on Nonne.[10]

In order to discuss the incidence and prevalence of multiple sclerosis in Turkey, I have collected statistics through official channels from all civilian and military hospitals and from the schools of medicine. It has been reported by the existing 44 clinics of neurology that between 1930 and 1952 only 619 patients, of whom 149 were women, had been hospitalized with this diagnosis several times. The five-year-interval incidences, showing the increase of cases during the last decades, are listed in Table 1.

The figures are, of course, smaller than the actual morbidity rate in the whole country, since most of the patients with this disease must have been treated in their homes by general practitioners or have not sought medical care and their disease has remained undiagnosed.

TABLE 1.—*Cases of Multiple Sclerosis Recorded in Turkey from 1930 to 1952, Showing Rates of Onset per 100,000 Population by Five-Year Periods*

Years	No. of Cases	General Population (Rough)	Rate per 100,000 Population
1930-1935	79	15,000,000	0.53
1935-1940	136	16,000,000	0.85
1940-1945	186	18,000,000	1.00
1945-1952	218	21,000,000	1.00

TABLE 2.—*Occupations and Locations of Patients with Multiple Sclerosis*

No. of Cases	Occupation	Villages	Towns	Port Towns
142	Farmers	102	28	12
124	Soldiers	92	18	14
106	Workmen	21	43	42
120	Housewives	62	26	32
64	Intellectual	2	32	30
13	Craftsmen	1	5	7
12	Tradesmen	..	3	9
13	Unknown	9	2	2
594		289	157	148

The geographic distribution of cases in Turkey shows that they are scattered through every part of the country almost proportionally with the population. By exception, there has been only one case in seven provinces of Anatolia, in the east, where the climate is warm (subtropical) and in the southwest, where the Mediterranean climate dominates. According to the average of temperatures for 22 years, these seven provinces are above the isotherm of 66 F. (19 C.) and below the 37-degree parallel. This result conforms to the observation of Limburg,[10] who claimed that multiple sclerosis is found very seldom below an isotherm of 66 F., and Steiner,[7] who stated that the disease is very infrequent below the 40-degree parallel in Europe.

The majority of the patients were inhabitants of villages or towns of central Anatolia and had not the opportunity to travel abroad or get in touch with foreigners. Most of the soldiers had left their villages for the first time in their lives. Only 11 patients of the series were foreigners, and seven had traveled to Europe. The localities with the occupations of the patients, are listed in Table 2.

The age distribution for 619 cases showed that the disease is rare before 20 and after 45 years of age and very rare before 15 and after 55, but there is a great increase between the ages of 20 and 40, with the maximum between 25 and 35 years.

The material of the larger hospitals was collected for clinical analysis. The total number of cases so collected was 410. Of the series of patients, 106 were females and 304 males.

In the family histories of these patients were found 18 with psychoses, 13 with epilepsy, 6 with oligophrenia, 10 with alcoholism, 20 with tuberculosis, 52 with vascular defects (paralysis, 31), and 10 with metabolic and 23 with allergic diseases. The past histories of the patients revealed malaria, 93; typhoid, 19; gonorrhea, 18; syphilis, 6, and several kinds of infectious diseases, including childhood fevers, 433. Sixteen of the patients described consanguinity, and 5 of them admitted that they were addicted to alcohol before they had multiple sclerosis. Twenty-six patients showed various manifestations of allergy.

In 29 patients, infectious diseases, such as malaria (18 patients), puerperal sepsis (1 woman), meningitis (2 patients), and typhoid (1 patient), preceded the

TABLE 3.—*Appearance of Complaints Relating to Various Systems in the Course of the Disease*

General Character or Localization of Complaints	Chronological Order and Per Cent of Cases			
	1	2	3	4
Sensorial	74	16	6	4
Motor	49	27	17	7
Urogenital	22	27	25	26
Cerebellar	30	28	22	20
Ocular	29	20	35	16

immediate onset of the disease. In 8 patients several kinds of operations, in 14 head trauma, in 4 head injuries with unconsciousness, and in 3 acute alcoholism preceded the appearance of symptoms. Three patients reported the sudden onset of the disease after electric shock (one patient), flight to an altitude of 5,000 meters (one patient), and intoxication with an unknown drug (one patient).

Among women who already had multiple sclerosis, 12 became worse after childbirth, whereas no difference was noticed in 4. Pregnancy was held responsible for the onset of multiple sclerosis by 7 women and childbirth by 19. Forty-one women with multiple sclerosis, however, had had one or more children in the years prior to the onset of their symptoms.

Psychogenic factors, such as worry, excitement of the wedding night, and the fear of earthquake and war, were claimed by 20 patients as responsible for the onset of their disease.

In the vast majority of cases the disease started at an early period of adult life. Three patients had their first symptoms before the age of 10 years. The onset of the disease dated back 1 to 5 years in 40%, 6-10 years in 41%, 11-15 years in 12%, and more than 15 years in 7% of cases. Among these, 10.8% of the patients showed rapid progression, and 45% slow progression, of their signs and symptoms. Remission occurred in 33.6% of the patients, and in 11.4% the disease was stationary.

According to the statements of the patients, the order of the appearance of complaints relating to various systems in the course of the disease are given in Table 3.

TABLE 4.—*Clinical Findings in 410 Reported Cases*

	Per Cent of Cases
Reflex disturbances	98.8
Deep reflexes of lower extremities increased	88.2
Abdominal wall reflexes diminished or absent	85.8
Babinski sign present	81.6
Ankle clonus present	46.8
Cremasteric reflexes absent	33.3
Mediopubic reflexes dissociated	28.5
Pharyngeal and palatine reflexes absent	25.6
Pupils slightly sluggish to light	19.3
Accommodation reflexes diminished or absent	5.0
Motor disturbances	90.0
Weakness of one or both lower extremities	86.4
Weakness of one or both upper extremities	26.2
Hypertonia	71.4
Gait spastic only	18.3
Gait spastic-ataxic	38.5
Gait ataxic only	15.2
Weakness of III, IV, and VI cranial nerves	15.2
Evidence of facial weakness	21.6
Weakness of other cranial nerves	14.4
Ocular manifestations	78.0
Nystagmus	78.0
Vision impaired	23.5
Temporal atrophy	19.9
Optic neuritis	16.4
Diplopia	13.3
Anisocoria	12.0
Rate of other manifestations	10.1
Disturbances of urogenital systems	67.3
Urological disturbances only	40.7
Genital disturbances only	26.6
Cerebellar disturbances	60.3
Tremor	59.4
Dysmetria	57.5
Dysarthria	38.4
Neurovegetative system disturbances	43.2
Neurovegetative dystonia	16.4
Sympathicotonia	14.6
Vagotonia	12.2
Sensorial disturbances	25.2
Objective disturbances in posterior column sensation	15.6
Changes in pain, temperature, and touch perception	9.7
Mental changes	24.6
Signs of neurosis	14.5
Other changes	10.1
Atrophy of extremities	9.6
Spinal tenderness	7.2
Convulsions	4.2

There was no peculiarity noticed in patients from the standpoint of their constitutions. None of the internal organs showed any important defect having a close relation to the disease. The neuropsychiatric symptoms and signs are tabulated in Table 4.

The laboratory examination of the blood and urine were within normal limits. Out of 281 benzoin tests of the cerebrospinal fluid, 110 atypical curves were obtained. Myelography of 61 patients and pneumoencephalography or ventriculography of 34 patients gave negative results. The capillaroscopic study of 34 patients showed that in the majority the capillaries were spastic and fragmented and the circulation was irregular.[17] The results of various therapeutic measures were not satisfactory.

SUMMARY

In this article the situation of multiple sclerosis in Turkey is studied, with a compilation of the etiologic and symptomatologic statistics on 410 cases that were collected from most of the larger hospitals.

Hospital records gave information on 619 patients with multiple sclerosis among residents of Turkey during the 22-year period from 1930 to 1952. The annual prevalence of cases is 0.2 per 100,000 population.

The geographic distribution of patients in Turkey shows that they are scattered through every part of the country almost proportionally with the population. By exception, there was only one case in seven provinces of Anatolia, where the Mediterranean (southwest) and subtropical (southeast) climate dominate. These provinces are above the isotherm of 66 F. (19 C.) and below the 37-degree parallel. The symptomatologic statistics of cases showed close parallelism with the statistics of the National Multiple Sclerosis Society.[18]

30 Yüksel Cd.

Dr. K. Keskinel prepared the observations on 52 patients who had been hospitalized at the Neurological Service of Ankara Medical Faculty, and Professor Saribaş gave permission to report the cases.

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Society Transactions

CHICAGO NEUROLOGICAL SOCIETY

Douglas N. Buchanan, M.D., *President*

Meyer Brown, M.D., *Vice-President*

Leo A. Kaplan, M.D., *Secretary*

Regular Meeting, Dec. 8, 1953

Residuals of Tuberculous Meningitis: Presentation of a Case. Dr. Meyer Brown and Dr. Louis Jensen (by invitation).

The history and findings in a case 36 months after onset of tuberculous meningitis were presented. The patient showed residuals and complications of tuberculous meningitis which were unusual in their number and severity. They consisted of impaired vision with optic atrophy, bilateral deafness, extensive weakness of the upper extremities and total paralysis of the muscles of the abdomen and lower extremities. Calculi had been removed from the bladder and left renal pelvis. Extensive decubiti had nearly healed. Despite the above, he had remarkable sparing of his mental faculties. It is of particular interest that he continued to show varying degrees of improvement in the majority of his complications and residuals.

Paraplegia Following Excessive Bishydroxycoumarin (Dicumarol) Therapy. Dr. Alex J. Arieff and Dr. Stanley W. Pyzik (by invitation).

A 53-year-old white male physician sustained an injury to the back of the calf, from which he developed an ascending thrombophlebitis. Twelve days after this injury a pulmonary embolus developed. Because of this he was put on heparin and bishydroxycoumarin therapy, 100 mg. of the bishydroxycoumarin being given daily. On the 16th and 17th days of bishydroxycoumarin therapy his prothrombin time was 62 minutes, at which time he developed a quadriplegia. His upper extremities recovered almost completely, but he still has severe spastic paraplegia, with paralysis of the bladder and bowel. He has had some sensory recovery, in a Brown-Séquard syndrome fashion, which is incomplete in the lower extremities.

It is now two years five months since the onset of his quadriplegia. He is severely disabled. The literature has no similar case, and it is because of the rarity and unusual nature of the disability that this report is rendered.

DISCUSSION

Dr. Paul C. Bucy: I am a little puzzled. We all agree that this man has a serious lesion of the lower spinal cord, but I am at a loss to understand why the syringomyelic disturbance is attributed so definitely to the bishydroxycoumarin therapy. Why might it not be the result of an embolism from the pulmonary infarct?

Dr. Adrien Verbrugghen: I had another view. I could not be sure that he might not have epidural hemorrhage. He had a high total protein.

Dr. Alex J. Arieff: Perhaps we should not have been so emphatic. The condition could have been a vascular occlusion (multiple) because he did have a pulmonary embolus. From the standpoint of an excess of bishydroxycoumarin, he had a prothrombin time of 62 minutes, which is way above the normal level. I could not see any other lesion than a hemorrhage of the cord. I do not see how the nature of the lesion can be proved without looking at the spinal cord.

He did not have any meningeal signs, tenderness, or spinal fluid block, thus ruling out an epidural lesion. The acute onset, with a transverse spinal cord lesion and a high prothrombin time, made the diagnosis of hemorrhage most probable.

DR. IRVING C. SHERMAN: How could an embolus give a transverse lesion of the cord? What vessels would be blocked?

DR. ALEX J. ARIEFF: It would be unusual. There would have to be multiple emboli in just one segment of the spinal cord.

Role of Apical Dendrites in Electrical Activity of the Cortex. DR. JAMES L. O'LEARY (by invitation), St. Louis.

Much recent experimental evidence indicates that both apical dendrites and cell bodies of cortical pyramids make significant contributions to electrical records of the cerebral cortex. In form of record and in the polarity of the electrical activity with respect to surface and white matter, consistent relationships can be established for both bodies and dendrites throughout a range extending from the most rapid evoked responses of single cells recorded intracellularly (Tasaki, unpublished observations) to slow direct-current changes, lasting for many seconds. In our own experiments this consistency includes evoked responses, convulsoid spikes, barbiturate spindles, and the direct-current after-effects of each.

Veratrine and strychnine applied topically to the cortex alter the responsiveness of the dendrite in opposite directions (i. e., the polarity). The action of veratrine is to lower the responsiveness of the apical dendrite, and as a result the depth-negative (surface-positive) components of the electrical records of activity are exaggerated. Strychnine exaggerates the surface-negative components of the cortical record, indicating, we believe, marked over-responsiveness of dendrites. For each of these oppositely reacting changes, redistribution of electrical charge along the long axes of apical dendrites and cell bodies is held responsible.

Injection of malononitrile, which releases cyanide ion and causes intracellular hypoxia, affects first the portion of the cortical potential assignable to dendrites. The part of the record attributable to cell bodies is more resistant. It is suggested that, besides hypoxia, other adverse toxic and metabolic alterations may find the dendrites the more susceptible at or above threshold effect.

DISCUSSION

DR. PERCIVAL BAILEY: We still do not know why the cortex is built in six layers, but studies of the individual layers by the technique used by Dr. O'Leary may ultimately enlighten us.

DR. JAMES L. O'LEARY, St. Louis: We believe that after-effects of evoked responses have more metabolic significance than do the fast disturbances from which they originate.

In reply to Dr. Bailey, depending upon one's frame of reference, even microelectrode recording from the interior of a cortical pyramid might be considered a gross effort. For example, no one has yet recorded from the interior of a dendrite. We may hope that some day even that will be possible.

Complications of Iodopyracet (Diodrast) Arteriography. DR. ADRIEN VERBRUGGHEN.

One hundred fifty angiograms were discussed in which there have been no untoward effects using 35% iodopyracet (Diodrast). These represented the author's first group of angiograms. Because of the lack of complications, the method of performing angiography was discussed in detail and at an operational level. Several points were made, of which the following is a summary:

Angiography seemed to give better results with general anesthesia induced by the percutaneous method.

The Sanchez-Perez machine lessened the necessity for using large amounts of iodopyracet.

There should be a delay between injections, during which the needle is left in place with a stylet.

A constant team should be used to perform the arteriographic studies, and not more than 20 cc. of 35% iodopyracet should be injected in one side at one sitting.

There were no other precautions taken in this group of cases.

DISCUSSION

DR. OSCAR SUGAR: What do you do with the needle in the 8 to 10 minutes before you make the succeeding injection?

DR. ADRIEN VERBRUGGHEN: I sometimes hold it. I put the obturator back into it and lay it on a gauze sponge.

DR. OSCAR SUGAR: We have had no such beautiful results as are reported here, results attributable to at least three things: (1) not injecting much of this poisonous material, iodopyracet; (2) waiting a long time between succeeding injections, and (3) doing nothing with the needle except plugging it with the obturator.

With intermittent saline injection, if a clot forms at the needle tip, that clot is pushed up into the cerebral circulation. These results are simply fantastic unless you know Dr. Verbrugghen and the carefulness with which he has done his work. Since he has instructed us, we have had no poor results in the last 200 carotid angiograms using iodopyracet.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

CEREBRAL METABOLISM DISTURBANCE AND DELIRIUM IN PERNICIOUS ANEMIA. D. C. SAMSON, S. N. SWISHER, R. M. CHRISTIAN, and G. L. ENGEL, A. M. A. Arch. Int. Med. **90**:4 (July) 1952.

This paper describes an investigation of the disturbance in cerebral function which occurs in pernicious anemia patients. The authors believe that certain disturbances in behavior in pernicious anemia patients are secondary to disturbances in cerebral metabolism, and that these are much more prevalent than has been recognized. These changes constitute a syndrome of delirium which can be clinically diagnosed by attention to the manifestations related to the reduction in the level of consciousness, particularly by specific testing of attention, memory, and capacity for abstract thinking. A second tool for the study of delirium is the electroencephalograph.

A series of 14 consecutive pernicious anemia patients admitted to a general hospital in hematologic relapse were studied. Of these 14 patients, delirium was found to be present in 13. The degree of delirium varied widely. The electroencephalograms in these 13 cases showed slowing in frequency of the waves, such as has been shown to be characteristic in delirium of many different origins. Neurologic evidence of some degree of spinal cord degeneration was found in 12 of the 14 patients. Thus, evidence of cerebral cortical involvement was as common as the better-known spinal cord disease.

By the use of serial mental status examinations and encephalograms before, during, and after treatment, it was demonstrated that the delirium and electroencephalogram began to improve about the time the reticulocyte response began, suggesting that the cerebral defect is a primary metabolic one, and not secondary to the anemia. With active treatment the defect in cerebral metabolism is reversible in most patients.

Samson and his co-workers point out that the electroencephalogram is a clinically useful and available tool for studying cerebral metabolic changes and following the course of therapy in pernicious anemia.

ALPERS, Philadelphia.

INCREASED INTRACRANIAL PRESSURE FOLLOWING RADICAL NECK SURGERY. R. K. JONES, A. M. A. Arch. Surg. **63**:599 (Nov.) 1951.

Radical dissection of the cervical lymph nodes with removal of the jugular vein causes increased intracranial pressure. This is particularly marked when both jugular veins are removed. After radical neck dissection 11 patients showed a considerable increase of lumbar spinal fluid pressure during an observation period of up to 12 days. The eyegrounds showed venous enlargement and blurring of the disk margins but no true choked disk. Some of the patients were drowsy and unresponsive immediately after the operation, but it was impossible to state whether this was due to increased intracranial pressure or to other factors, such as medication. For prevention of untoward reactions the author suggests that the patient be kept in the upright, sitting posture immediately after surgery. Tight neck dressings must be avoided; especially, the jugular vein on the intact side should not be compressed. Intravenous administration of hypertonic solutions are beneficial, but lumbar puncture is inadvisable.

LIST, Grand Rapids, Mich.

THE CHANGES IN CEREBRAL VASCULAR RESISTANCE OF MAN IN EXPERIMENTAL ALKALOSIS AND ACIDOSIS. J. F. SCHIEVE and W. P. WILSON, J. Clin. Invest. **32**:33 (Jan.) 1953.

In this study the effect on cerebral vessels of changes in pH and CO_2 content was investigated. By intravenous infusion $NaHCO_3$ and NH_4Cl, metabolic alkalosis and acidosis, respectively, were produced in man. The changes which occurred in cerebral blood flow and cerebral vascular resistance were noted and compared with the changes previously reported after respiratory acidosis and alkalosis.

Schieve and Wilson found that metabolic alkalosis, as produced by giving 3% $NaHCO_3$ solution intravenously, increased cerebral blood flow 65% above resting normal values; isotonic bicarbonate solution (1.2%) causes a 30% increase. The increase in cerebral blood flow after $NaHCO_3$ is not primarily due to changes in intravascular volume because an equivalent degree of hemodilution produced by the infusion of isotonic NaCl solution does not cause an increase in cerebral blood flow. Infusion of 2% NaCl solution does cause a demonstrable increase in cerebral blood flow. It is not of the order of magnitude produced by the infusion of an equally hypertonic solution of $NaHCO_3$. Intravenous infusion of 0.8% NH_4Cl solution reduced cerebral blood flow approximately 20 to 25%.

These studies, when coupled with previous studies of Kety, show that, in the absence of anoxia, cerebral vascular tone is more closely related to the total CO_2 content of arterial blood rather than arterial pH levels.

ALPERS, Philadelphia.

THE EYE AND THE DIENCEPHALON: XII. REACTIONS OF INTRAOCULAR PRESSURE AND RETINAL ARTERIAL PRESSURE TO CORTICAL AND MESENCEPHALODIENCEPHALIC DEPRESSORS. A. RUBINO and I. ESENTE, Riv. oto-neuro-oftal. **25**:351 (Sept.-Oct.) 1950.

In a group of normal controls, i. e., patients with arterial hypertension and others with glaucoma, Rubino and Esente noted a definite diminution of intraocular pressure and retinal arterial pressure with hypnotic doses of barbiturates. The drop in retinal arterial pressure was the more striking, the action probably due to inhibition of diencephalic activity. Larger or narcotic doses of barbiturates increased the retinal arterial pressure to somewhat above normal. The intraocular tension, however, remained below normal. The use of inhibitors of the cerebral cortex, such as chloralhydrate, brought a moderate increase in retinal arterial pressure and a slight increase in intraocular pressure. The removal in a patient of the activity of the cortex, which probably inhibits diencephalic function, permits the latter to act without control. This results in both an increase in the tone of retinal vessels and an increase in intraocular pressure. Maximal doses of barbiturates completely paralyze the diencephalic centers and allow peripheral physical and chemical stimuli alone to determine the tone of the vessels and the pressure within the eyeball.

N. SAVITSKY, New York.

Diseases of the Brain

RESIDUAL EFFECTS OF RICKETTSIAL DISEASE ON THE CENTRAL NERVOUS SYSTEM. M. J. ROSENBLUM, R. L. MASLAND, and G. T. HARRELL, A. M. A. Arch. Int. Med. **90**:444 (Oct.) 1952.

Rocky Mountain spotted fever is one of the severest of all infectious diseases. Essentially it is a specific generalized intracellular infection of small peripheral blood vessels. Pathologic examination reveals greater damage to the brain in Rocky Mountain spotted fever than in any other Rickettsial disease. In the central nervous system areas of demyelination may be found adjacent to or removed from the vascular lesions.

The acute phase of the infection is most frequently ushered in by headache, which may develop before the rash appears. As the disease progresses, mental confusion, dulling of the senses, restlessness, or lethargy progressing to coma may be noted. Muscular twitchings, purposeless movements, fibrillary tremors, and abnormal neurologic signs, such as ankle clonus or a positive Babinski reaction, may occur. The picture is often one of encephalitis.

It is difficult to estimate the extent of the acute lesions and the degree of residual damage in the central nervous system, since the involved areas are so small and are diffusely scattered. Neither the clinical findings nor studies on the spinal fluid during the acute phase of the illness make it possible to predict which patients will be left with permanent damage to the nervous system. After convalescence, residual brain damage may be manifested clinically by loss of memory, pronounced mental retardation, behavior disorders, or even convulsions. The observation of seizures led Rosenblum and his colleagues to undertake this study in an effort to determine the frequency and character of the sequelae in the central nervous system.

Thirty-seven patients, of all ages, who had recovered from Rickettsial spotted fever were reexamined one to eight years after the acute phase of the illness. Evidences of residual neurologic damage were sought in the history, physical examination, and electroencephalogram.

At the time of reexamination, 21 of the 37 patients had some type of neurologic sequela. Fourteen patients gave a history of symptoms related to the central nervous system: Six had neurologic signs, and 12 had clearly abnormal electroencephalograms. Twelve additional patients had borderline electroencephalographic abnormalities. The electroencephalogram was abnormal in a high proportion of patients who had fever for more than 10 days.

Of 15 patients who had been observed to have abnormal neurologic signs during the acute illness, 3 had residual signs, and 2 were having convulsions. Seven of these patients had abnormal electroencephalograms; four had borderline tracings, and four showed no electroencephalographic changes.

Of 24 patients who received supportive therapy alone (including those treated with antiserum or paraaminobenzoic acid), 14 had neurologic sequelae of some sort; these sequelae were severer than those seen in patients who received antibiotic therapy. Of the 13 patients treated with antibiotics, 6 had evidences of residual neurologic damage. Only one of seven patients receiving antibiotics within the first three days of rash had an abnormal electroencephalogram.

Necropsy was performed on eight patients who died during the acute illness. Microscopic evidence of damage was found in all six patients in whom the brain was examined. In these patients microinfarcts or granulomas were found adjacent to cerebral blood vessels.

Attention is called to the recent work of Arney on the use of corticotropin and cortisone in Rocky Mountain spotted fever. A short course of these hormones administered simultaneously with antibiotics has decreased the febrile period even more than antibiotic therapy alone. Whether such treatment will serve to reduce the extent or frequency of sequelae in the central nervous system is unknown.

ALPERS, Philadelphia.

INSENSITIVITY TO PAIN AS A COMPLICATION OF PHENURONE THERAPY IN EPILEPSY. FRANCIS M. FORSTER and KALMAN FRANKEL, Dis. Nerv. System **11**:24-26 (Jan.) 1950.

This report presents analgesia as an unusual complication of phenacemide (Phenurone) therapy in epilepsy. A 33-year-old man had suffered from generalized seizures every three months for eight years and from weekly spells of vertigo since an apparently minor head injury five years before. These minor episodes had been decreased in frequency but increased in severity by use of diphenylhydantoin (Dilantin). Neurological examination was normal; specifically, there was no impairment of perception of pinprick or temperature. Laboratory studies were noncontributory. The EEG showed diffuse spiking, especially under pentylenetetrazol (Metrazol) activation. Mesantoin and phenobarbital failed to control his convulsions; and, with the addition of diphenylhydantoin to his regimen, the patient developed toxic signs, relieved by withdrawal of the latter drug. He was then tried on phenacemide alone. Within a week he complained of disturbed memory and concentration, feelings of unreality, itching of the scalp, and numbness of the extremities. The patient had been burned on the right arm by a bit of hot metal, with no recognition of the injury, until he noted the odor of burned flesh. Upon discontinuation of phenacemide this lack of sensation disappeared. It is pointed out that the EEG studies in this case did not indicate a temporal lobe dysrhythmia, as described by Gibbs for patients becoming psychotic during phenacemide treatment; nor was there any focal discharge in the sensory cortex. A cortical topical relationship as a cause of the phenomenon is therefore not substantiated, and it remains unexplained.

BEATON, Tucson, Ariz.

ASTROCYTOMA OF FIFTEEN YEARS' DURATION: A CASE REPORT. ARTHUR WEIL, J. Neuropath. & Exper. Neurol. **11**:409 (Oct.) 1952.

Weil reports a case which is unusual for its long survival period (15 years) following the removal of a cerebral neoplasm which had been diagnosed, histologically, as astrocytoma. It is also unusual for the fact that, in the course of this long period of survival, the brain tumor recurred and grew to involve the whole left half of the cerebrum, including the corpus callosum, and most of the left half of the brain stem.

Autopsy findings disclosed several histologic types of astrocytoma in the tumor: fibroblastic, giant cellular, and spongioblastic. No transition into glioblastoma (spongioblastoma) multiforme was present, and no mitotic figures were seen. In addition, there were formations of an oligodendroglioma and a neuroblastoma. There was some relationship between the anatomic structure

affected and the histologic type of the tumor. The fibrillary type, with the formation of a dense glial meshwork, was predominant in the cerebral hemisphere; the spongioblastic type, in the midbrain and upper pons; the gigantocellular type, the oligodendroglioma, and the neuroblastoma were found in sections of the diencephalon.

ALPERS, Philadelphia.

RUSSIAN SPRING-SUMMER ENCEPHALITIS. G. A. JERVIS and G. H. HIGGINS, J. Neuropath. & Exper. Neurol. **12**:1 (Jan.) 1953.

Russian spring-summer encephalitis is a disease endemic in certain far-eastern provinces of Russia. In man three clinical forms are recognized: (*a*) abortive infections, causing fever for three to five days and ending in full recovery; (*b*) meningoencephalitic forms of moderate severity, followed by recovery in 80% of cases and by permanent neurological sequelae in 20% and (*c*) severe fulminating meningoencephalitis, with death usually occurring within one to seven days. The disease is caused by a virus. The vector of the virus is a tick, and possible natural reservoirs of infection are small rodents and birds. No reports of the disease in the human have appeared outside of Russia.

The authors describe a patient who contracted Russian spring-summer encephalitis while engaged as a laboratory assistant in experimental work intended to investigate the effect of Russian encephalitis virus upon experimental tumors in mice. The patient fed and handled the infected animals under strict precautions usually carried out in this type of work. At no time did she report any laboratory accident, such as puncture wound or breaking of a virus ampule.

The clinical picture presented was one of rapidly fatal acute encephalitis and corresponded closely to the fulminating form of spring-summer encephalitis described by the Russian investigators. The sudden death, which occurred on the fourth day of illness, suggested bulbar involvement. The results of neutralization tests showed that the virus isolated from brain material of the patient was identical with Russian spring-summer encephalitis virus.

The pathological examination indicated a widespread involvement of the gray matter, with selectivity of the lesions for the motor cortex, cerebellum, medulla, and spinal cord. The authors point out the similarities between the lesions of Russian encephalitis and those experimentally produced by louping-ill virus.

ALPERS, Philadelphia.

LOCALIZATION OF INTRACRANIAL LESIONS BY RADIOACTIVE ISOTOPES. W. T. PEYTON, G. E. MOORE, L. A. FRENCH, and S. N. CHOU, J. Neurosurg. **9**:432 (Sept.) 1952.

The authors have previously reported their earlier experiences in localizing brain tumors by the use of radioactive isotopes. In their first series 62% were correctly localized, and in their second, 65%. In the present series, of 71 cases, they have used radioactive iodinated human serum albumin and a new type of Geiger-Müller tube.

They conclude that approximately 70% of intracranial tumors can be correctly localized by radioactive isotope examination alone; but if the clinical data are utilized in the interpretation of radioactive isotope counts, correct localization is very much enhanced, up to 94%.

There are biological limitations to this method which lead to erroneous diagnoses unless the clinical data are utilized in the interpretation. Cystic and necrotic lesions do not take up the radioactive isotope and therefore may give a false localization, with low counts over the lesion. Small lesions do not take up enough of the dye to give a good differential count over the lesion, and certain types of tumor, especially oligodendroglioma, appear to take up the isotope very little. Midline lesions (frequently they are also small) and posterior fossa lesions are difficult to localize. Lesions other than tumors, but which lower the blood-brain barrier, such as vascular lesions, and possibly inflammatory and demyelinating lesions, give a focus of high counts. Therefore this procedure does not differentiate between a neoplastic and a non-neoplastic lesion.

The most easily localized lesions with isotope encephalometry are large lesions in the cerebral hemisphere associated with edema. Glioblastoma, meningioma, and metastatic tumors give the best differential counts.

ALPERS, Philadelphia.

ELECTROENCEPHALOGRAPHIC STUDIES IN CEREBRAL ANGIOMA. D. P. ROSENBERG, J. Neurol., Neurosurg. & Psychiat. **15**:260 (Nov.) 1952.

Rosenberg analyzed the electroencephalograms in 55 cases of proved cerebral angioma. He found that the EEG gave a lateralizing or localizing indication in 67% of the cases, the usual findings being localized 6 to 7 cps activity and/or high-voltage 2 to 3 cps waves showing phase reversal over the site of the lesion. These changes, with minor variations, are usually seen with other forms of cerebral tumor.

In discussing the value of electroencephalography as a diagnostic aid in angioma, the author notes that no specific EEG disturbance diagnostic of angioma could be seen in the 94 records of the 55 patients. In general, an angioma gives an EEG picture similar to that of cerebral tumor, which characteristically shows localized high-voltage irregular delta waves. However, the impression is that, with angioma, increased intracranial pressure and the spread of edema play, on the whole, a less important part than in cases of tumor, giving less generalized delta activity that will obscure a true focus and allowing a clearer localization of the intermediate slow activity. The same distinction serves to differentiate angioma from cerebral abscess, where, in addition, the slow delta waves at ½ to 2 cps are usual. The determination of pathology by the EEG is at best uncertain.

ALPERS, Philadelphia.

MENINGIOMAS OF THE POSTERIOR FOSSA. D. PETIT-DUTAILLIS and S. DAUM, Rev. neurol. **81**:557, 1949.

Petit-Dutaillis and Daum report 41 cases of meningioma of the posterior fossa, in 21 of which it was in the lateral recess. They report their observations on the latter type. They classify the tumors on the basis of site of rather than of dural attachments. The authors point out that the site is less important in the clinical picture than the direction of growth. In five of the cases only did the meningioma resemble an acoustic neuroma, but in two of them the authors believe that the diagnosis could have been made from the hyperostosis of the petrous ridge, which was clearly discernible. They point out that this sign is highly indicative of meningioma. In one case erosion of the petrous ridge was demonstrated.

Clinically, the diagnosis was easy in three of the cases by virtue of the small size of the tumor and its origin at a point of exit of a cranial nerve. The other cases have few points in common, but the authors note the high frequency (50%) of involvement of the 9th and 10th nerves early in the course of the disease, and occasionally of the 11th and 12th. This is true also of other tumors of the lateral recess. In 33% of cases there was bilateral involvement of the fifth nerve: corneal areflexia, or occasionally hypesthesia, on one side and hyperalgesia, or even tic douloureux, on the other, due to a subpontine tongue of the tumor.

Surgically, the tumors constitute a difficult group, with large dural adhesions over the sinuses and often over the brain stem. They are hard and very vascular. The operative results were poor and entailed high immediate and long-term mortality, due to the necessity of leaving much of the growth untouched. In the cases of successful surgical intervention there were many sequelae. The authors state that an attempt at complete removal of the tumor should almost never be made.

LEGAULT, Washington, D.C.

SUPRASELLAR CHOLESTEATOMA. P. DESVIGNES and MICHEL BRUN, Rev. oto-neuro-opht. **24**:175 (April) 1952.

Eight cases of suprasellar cholesteatoma, including one previously reported by the authors, were found in the literature. Desvignes and Brun report an additional case in order to illustrate the possible importance of destruction of one posterior clinoid process in the diagnosis of this rare affection.

The first case was that of a man aged 29 with a history of progressive diminution of vision for one year, bilateral primary optic atrophy, and a bitemporal field defect. There were no hypothalamic or pituitary changes. The spinal fluid, but not the blood, gave a positive Wassermann reaction. Surgical exploration revealed a cholesteatoma, which was completely removed. Vision, however, did not improve. An x-ray of the skull showed a normal sella except for a defect in one of the posterior clinoid processes.

The second case was that of a woman aged 37 who had become aware of diminished vision in the right eye 16 years previously. Treatment was ineffective. Optic nerve atrophy was found on the right when the patient was seen for treatment of bitemporal and supraorbital headaches and recent diminution of vision in the left eye. Primary optic nerve atrophy was found on the right; the left disk was pale, with normal visual acuity ($\frac{1}{10}$ in the right eye and $\frac{10}{10}$ in the left eye). Polydipsia, sexual frigidity, and amenorrhea had been present for two years. X-ray examination of the skull showed changes in the sella turcica and absence of one posterior clinoid process. Exploration showed a tumor compressing the right optic nerve. The tumor was the size of a nut and proved to be a cholesteatoma. Three months later there was no change in visual acuity. The patient had two subsequent attacks of sudden complete blindness of the left eye without changes in the fundi. These attacks were considered by the authors to be due to coincidental optic neuritis.

Hypophyseal and hypothalamic changes need not be absent in cases of suprasellar cholesteatoma. X-ray changes in the optic canal may not be present unless the tumor invades this region. The authors suggest the possible diagnostic value of the change in one posterior clinoid process.

N. Savitsky, New York.

Diagnosis of Spheno-Occipital Chordoma. D. Petit-Dutaillis; R. Messimy, and Benjhain, Rev. oto-neuro-opht. **24**:202 (May-June) 1952.

The authors review the clinical features of spheno-occipital chordoma on the basis of the literature and a study of four personal cases. Three of these chordomas were encountered among 3,390 brain tumors at the neurologic and neurosurgical service of La Pitié. There was no question of the histologic diagnosis in any of the cases. In none of the four cases was the diagnosis made preoperatively. The chordomas, at least in their early stages, presented the clinical picture of a tumor in the anterior part of the skull. In three of the cases the clinical picture corresponded to the description in the literature. The presenting complaint was frontal and orbital headache, unilateral or bilateral diminution of vision, or involvement of the third or fourth nerves. In one of these cases there were recurring episodes of transitory oculomotor paralyses and headache over a few months. The clinical picture was that of chiasmal compression with a midline tumor syndrome, usually with unilateral ocular paralyses and occasional involvement of the fifth nerve. The seventh and eighth nerves were involved in only one case. This syndrome of chiasmal and unilateral oculomotor paralysis remained unchanged in one case for six years before evidence of extension to the posterior fossa appeared. The authors note that in two of the three cases the left side was more involved than the right. This tendency to left-sided extension has been noted previously. In one case there was involvement of the olfactory nerve due to anterior extension of the tumor. In two cases hearing defects and anosmia were due to extracranial extension of the tumor into the pharynx and nose. In one case mental changes and mild unilateral pyramidal tract signs suggested a frontal tumor; but there was extensive sellar destruction without calcification. Ventriculogram showed obliteration of the anterior two-thirds of the third ventricle, and a preoperative diagnosis of craniopharyngioma was made. In one case the tumor extended into the orbit. In two cases a diagnosis of chordoma was made preoperatively, but the lesions proved to be a chondroma of the clivus and an osteosarcoma at the base. Suprasellar calcification in the chordoma is usually in the form of small triangular or quadrangular spots, at times appearing linear when seen laterally; these calcifications are more suggestive of bony fragments than of calcifications within a tumor. In one case the shell of the tumor was demonstrated clearly by tomography. The authors recommend tomography for more careful study of the pseudocalcifications which are really bits of bone dragged along with the growing tumor mass. The x-ray picture of calcification in chondroma is distinctly different and can be used in differential diagnosis. The complete absence of calcification with extensive destruction of bone at the base of the skull is in favor of sarcoma. The importance of examination of the nose and throat is emphasized. In one case a biopsy of the tumor within the nose gave the clue to the diagnosis before operation.

N. Savitsky, New York.

ELECTROENCEPHALOGRAPHIC STUDY OF TWENTY CASES OF POST-TRAUMATIC SUBJECTIVE SYNDROMES IN OLD HEAD INJURIES. P. VERCELLETTO; H. GIROIRE; A. CHARBONNEL, and J. COLAS, Rev. oto-neuro-opht. **25**:101 (Feb.-March) 1953.

The authors report an electroencephalographic study of 20 patients who had subjective complaints due to old head injuries. The clinical picture in each case was that of a postconcussion syndrome. All the patients were normal from the neurological, ophthalmological, and otological standpoints. None of the patients had seizures. The injuries had taken place two months to two years before the investigation. The electroencephalographic studies were done with a standard technique, using 21 electrodes. Hyperpnea and photic stimulation were tried in each case. The electroencephalographic records of seven patients were normal. Seven other patients showed diffuse electrical changes with theta and delta waves replacing alpha rhythms; the waves were increased by hyperpnea. The abnormal waves were most prominent in the frontotemporal regions. In a few others, there was bilateral beta waves (20 to 30 cps). Three patients presented foci of abnormal activity with spiked waves and phase reversals. Three patients showed disorganization of normal waves with frequent bursts of delta activity, sometimes bilateral and at others predominating in one hemisphere.

No correlation of the severity of the subjective syndrome and the electrical abnormalities was found. Severe subjective complaints may be present with a normal electroencephalogram. There is a difference of opinion as to when these tracings become normal; during the first few weeks all patients who sustain a concussion show some abnormality.

N. SAVITSKY, New York.

RETRACTION NYSTAGMUS AS A FOCAL SIGN. V. TRONCONI, Riv. oto-neuro-oftal. **24**:195 (March-April) 1949.

Twelve cases of retraction nystagmus have appeared in the literature since it was first described by Körber, in 1903. A girl aged 14 complained of headaches and vomited frequently. She had attacks of mental dulness and brief periods of loss of consciousness. No abnormal movements were noted. In her admission to the hospital, there was paralysis of the right external rectus muscle and of upward conjugate gaze. The Roth-Bielchowsky reflex was intact. During convergence and with upward gaze retraction of the eyeball was noted. An extensor response was elicited on stimulation of the soles, and an Oppenheim sign was present bilaterally. The patient fell backward when standing up. Papilledema was present bilaterally. Retraction nystagmus was noted after the nystagmus induced by vestibular tests ceased. Optokinetic nystagmus with lateral movements was normal after the retraction nystagmus was noted. Optokinetic nystagmus was absent with upward gaze and was intact with downward gaze. Retraction nystagmus was present during optokinetic tests with upward and downward gaze. Ventriculography revealed marked dilatation of both lateral ventricles and the third ventricle. Iodoventriculography showed incomplete closure of the aqueduct. The ventricular fluid gave a mildly positive Pandy reaction, and contained two cells per cubic millimeter and 33 mg. of protein per 100 cc. The child died but autopsy was not performed. Retraction nystagmus is considered to indicate a lesion in the mesencephalon in the region of the supranuclear oculomotor pathways. The resulting defect in innervation causes simultaneous contraction of agonists and antagonists, producing retraction of the eyeball rather than movement in a normal direction.

N. SAVITSKY, New York.

PUPILLARY REFLEXES IN MONOZYGOTIC TWINS. V. CIMA, Riv. oto-neuro-oftal. **26**:287 (July-Aug.) 1951.

Lowenstein described four types of pupillary action, considered to be normal variants and, according to him, hereditary in character. Identical pupillary reactions have been noted by Lowenstein in monozygotic twins. Cima studied three pairs of identical twins in an attempt to corroborate these observations. Pupillary reactions were studied by means of the pupillograph of Borsotti, modeled after Lowenstein's instrument. Only the direct reaction to light was studied. In two of the pairs of identical twins there was a marked difference in the initial size of the pupils, indicating a difference in the tone of the muscles of the iris. A decided difference in the

latent period was noted in the third pair. The type of curve was not the same in any pair of identical twins. It was evident the curves were not even approximately superimposed. There was also a difference of degree of the pupillary response in identical twins. These findings do not corroborate the statements of Lowenstein that the pupillary reactions to light are hereditary.

N. SAVITSKY, New York.

EARLY DIAGNOSIS OF PARKINSON. ROBERT WARTENBERG, Arq. neuro-psiquiat. **10**:139 (June) 1952.

Wartenberg suggests the term Parkinson rather than Parkinsonism. He denies that Parkinsonism can exist without rigidity. Rigidity may appear first, without tremor. Rigidity usually begins in the head region. The head-dropping test is recommended as a valuable early sign. The patient lies supine. The head is suddenly lifted up and then dropped. When tonus of the head muscle is increased, the head drops slowly. If the head drops normally, Parkinsonism can be excluded.

In early Parkinsonism, forward excursion of the arm while walking may be diminished on one side only. Wartenberg suggests that this may be appraised more easily if the examiner, keeping pace with the patient, walks abreast of him and watches him from the side. No other disease of the nervous system reduces pendulousness of an extremity so early and so obviously as does Parkinsonism. Only deviations found on repeated examinations are of value.

In the shoulder-shaking test the examiner places his hands on the patient's shoulders and gently rocks the trunk back and forth. Swinging of the upper limbs results. In unilateral Parkinsonism the swing is diminished on the affected side. The examiner can gradually reduce the force and range of the jerks. This causes a reduced shoulder movement and consequently reduces pendulousness. The examiner finally reaches a point where only one arm swings and the other arm remains static. Shoulders may be swung simultaneously or alternately.

In the arm-dropping test both upper limbs are suddenly thrown upward by the examiner as he stands in front of the patient and slides his hands between the patient's chest and arms. The upper limbs are allowed to drop. In unilateral Parkinsonism the fall of one arm is retarded on the affected side.

The pendulousness of the legs is tested by seating the patient on a table, with his lower limbs relaxed. The patient's legs are lifted and allowed to drop, the examiner observing the length of time that they swing. In unilateral Parkinsonism the diminished swinging of the affected limb is striking. It may be the earliest sign of involvement of the lower limb.

Wartenberg adds a few other signs of some value—exaggeration of contraction of the orbicularis by tapping the glabella gently with a reflex hammer; defective convergence of the eyes, especially in the postencephalitis form; abnormal posturalization of the hands and fingers, especially of the thumbs; clumsiness of fine finger movements; tightening of the biceps muscle with flexion of the forearm; deviation of the arms inward and downward when extended, and micrographia.

N. SAVITSKY, New York.

Diseases of the Spinal Cord

CLINICAL SIGNIFICANCE OF SOME CONGENITAL CHANGES IN THE OPTIC DISK. ARTHUR J. BEDELL, J. A. M. A. **151**:95 (Jan. 10) 1953.

Before discussing some of the congenital changes of the optic disk, the author reviews the wide physiological variations in size, color, and general configuration which may occur in the so-called normal disk. He calls especial attention to the relations of the central excavation to the early diagnosis of glaucoma, papilledema, and papillitis.

The congenital anomalies discussed include medullated nerve fibers, remnants of Cloquet's canal, vestiges of Bergmeister's papilla and unusually large residues, falciform folds of the retina, pseudo-choked-disks, inverted disk, "holes" or "pits" in the disk, some staphylomas, posterior vortex veins in or close to the margin of the scleral rim, and congenitally abnormal vessels. Several illustrative plates are shown.

ALPERS, Philadelphia.

NEOPLASMS OF CENTRAL NERVOUS SYSTEM SIMULATING DEGENERATIVE DISEASE OF THE SPINAL CORD. H. R. OBERHILL, ROGER A. SMITH, and PAUL C. BUCY, J. A. M. A. **151**:612 (Feb. 21) 1953.

The frequency of simulation of degenerative diseases of the nervous system by neoplasms and other space-occupying lesions makes it imperative that these remediable lesions be recognized promptly so that the patient's condition need not continue to deteriorate under the hopeless diagnosis of one of the degenerative diseases.

Five illustrative cases are presented by Oberhill and his co-workers. The first case was more suggestive of subacute combined degeneration of the spinal cord than it was of tumor, but the patient proved to have an intradural meningioma, which was removed. The second patient had subacute combined degeneration of the spinal cord plus a hemangioblastoma of the cerebellum and showed considerable improvement after removal of the tumor. In the third case an extramedullary neoplasm of the cervical spinal cord produced a clinical picture strongly suggestive of amyotrophic lateral sclerosis. In the fourth case an intraspinal tumor was mistaken for multiple sclerosis by competent neurologists and neurological surgeons for several years. This case demonstrated the fact that intraspinal neoplasms may be associated with remissions and relapses and that the absence of a steadily progressive course does not exclude the possibility of an intraspinal tumor. The fifth case was also one of an intraspinal tumor manifesting its presence with intermittent symptoms and the condition had previously been diagnosed as syringomyelia by one neurologist and multiple sclerosis by another.

These cases, and others in the literature, demonstrate certain points of importance which will help avoid errors. The initial history and general physical and neurological examinations must be thorough and complete. Whenever a diagnosis of a degenerative disease has been made, the patient should be seen at regular intervals, careful notes made of the course of the disease, and the patient examined repeatedly.

It has been held that a myelogram is not indicated in the absence of evidence of obstruction of the spinal subarachnoid space on Queckenstedt's test. The authors show this is false in the present series of cases and quote other authors whose findings support theirs. Myelography, on the other hand, may fail to reveal the presence of an intraspinal tumor.

Pain and sensory changes are so often associated with intraspinal tumors that they are sometimes considered essential to such a diagnosis. This is not the case, as illustrated by the third case in this series. Space-taking lesions lying anterior to the spinal cord are particularly likely to produce only motor symptoms without sensory alterations and thus lead to confusion with amyotrophic lateral sclerosis or multiple sclerosis.

Though roentgenograms of the skull and spine are often of value in diagnosing neoplasms of the central nervous system, negative roentgenograms are meaningless. The diagnostic evidence presented by x-ray examinations of the vertebral column is often unremarkable. Among the most valuable findings are widening of the spinal canal and erosion of the vertebral pedicles.

These workers feel that in every case in which signs of involvement of the spinal cord can be explained by a single well-localized lesion but without the other evidences of an intraspinal tumor, the advisability of an exploratory laminectomy must be seriously considered. It is better to err on the side of a seemingly unnecessary exploration rather than leave a remediable lesion untreated.

ALPERS, Philadelphia.

DUMBBELL (HOURGLASS) NEUROFIBROMAS AFFECTING THE SPINAL CORD. J. G. LOVE and H. W. DODGE JR., Proc. Staff Meet., Mayo Clin. **27**:249 (June 18) 1952.

Sixty cases of dumbbell neurofibroma which affected the spinal cord and adjacent paraspinal structures were analyzed and the pertinent literature reviewed.

Characteristically, the spinal part of these tumors produced symptoms of cord compression when they occurred in the thoracic portion of the spinal cord. At the lumbar and lumbosacral levels of the spinal cord the symptoms were those of progressive failure of a nerve root, while at the cervical level the symptoms often were those of a combination of root failure and compression of the spinal cord. Symptoms arising from the extraspinal portion of the tumor varied with the level of the lesion and the nature of the paraspinal structures affected. Dumbbelling of these tumors occurred most frequently on the dura mater and through the intervertebral foramen.

Most commonly, roentgenologic evidence of the dumbbell tumor consisted of an enlarged, smoothly eroded intervertebral foramen. Examination of the cerebrospinal fluid frequently revealed incomplete or complete obstruction of the subarachnoid pathways of the spinal fluid and a value of more than 100 mg. of protein per 100 cc. of spinal fluid. Pathologically all the tumors were neurofibromas. Malignant degeneration occurred definitely in one case and questionably in a second case.

All the tumors studied were amenable to surgical treatment, most of the dumbbell neurofibromas affecting the spinal cord lending themselves to one-stage removal. The average follow-up period after operation was 77 months. Dumbbell neurofibromas (neurilemomas) were found to be extremely benign, not infrequently occurring as neoplasms affecting the spinal cord and the paraspinal structures. The prognosis for recovery after complete removal of the tumor is excellent.

ALPERS, Philadelphia.

SYNDROME OF RADICULAR COMPRESSION DUE TO PROMINENT LIGAMENTUM FLAVUM. ORLANDO SATTAMINI-DUARTE, Arq. neuro-psiquiat. **11**:145 (June) 1953.

Sattamini-Duarte reports a case in which the differential diagnosis of herniation of a disc and the effects of a thickened yellow ligament was difficult. A 47-year-old man was hospitalized with a complaint of severe pruritus over the left foot for about three months. A few days after the onset he began to complain of severe pain in the inferior half of the anterolateral aspect of the left leg. He also found it impossible to flex the left foot. Soon after the onset he noted that hyperextension of the left thigh caused pain in the left buttock, which radiated to the left popliteal region. The pain then began to radiate down the anterolateral aspect of the left leg, ending in the dorsum of the left foot.

Neurological examination soon after admission to the hospital showed intermittent claudication on the left, weakness of the left toes, hypotonia and mild atrophy of the muscles of the left foot and leg, and difficulty in eliciting the left ankle jerk. There was absence of response to pain, touch, and temperature stimuli in the soles and inner surfaces of the legs. Pressure over the upper sacrum caused pain. The spinal fluid examination was negative. X-rays of the lumbar spine showed nothing significant. Myelography showed a deformity just above the fourth and fifth lumbar vertebrae. A left hemilaminectomy revealed no herniated disc; the ligamentum flavum was thickened (5 mm.) and was pressing against the roots posteriorly; 2 cm. of the ligament was removed; there were no adhesions. Histological studies showed the yellow ligament to be thickened, with no degeneration or other pathologic changes. After the operation the pain and sensory changes cleared up completely. Four months later the patient showed very slight impairment of dorsiflexion of the left foot and slight hypotonia of the left leg; there was no pain in the back or left lower limb.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

A STUDY OF THE NUTRITIONAL DEFECT IN WERNICKE'S SYNDROME. G. B. PHILLIPS, M. VICTOR, R. D. ADAMS, and C. S. DAVIDSON, J. Clin. Invest. **31**:859 (Oct.) 1952.

This study was designed to define more clearly the effect of bed rest, withdrawal of alcohol, and administration of vitamins on the individual clinical signs comprising Wernicke's syndrome. Nine patients with typical manifestations of this syndrome were maintained for varying periods of time on a purified diet consisting solely of glucose and minerals. At appropriate times specified vitamins were added. The principal components of the clinical picture, i. e., the ophthalmoplegia, nystagmus, ataxia, and mental disturbances, were examined at frequent intervals.

Phillips and his co-workers found that prior to the administration of thiamine there was no improvement in any of the signs. Despite alcohol withdrawal, bed rest, and the addition of other vitamins (nicotinic acid, calcium pantothenate, pyridoxine, folic acid, ascorbic acid, riboflavin, B_{12}), the ophthalmoplegia progressed and the ataxia remained unchanged, while the nystagmus decreased only in association with an increase in ocular paralysis. When thiamine only was added to the purified diet, the ophthalmoplegia cleared considerably in from one and a quarter to six hours; diminution in nystagmus and ataxia also occurred in some of the patients, but the change was more gradual; there was improvement in mental disturbance, but it was minimal in degree.

From their observations the authors conclude that the ophthalmoplegia of Wernicke's syndrome is related to a specific lack of thiamine. The nystagmus and ataxia also appear to be related to thiamine deficiency, but the evidence is less conclusive. No definite conclusions can be drawn regarding the relationship of the mental disturbances to the deprivation of thiamine or other vitamins.

ALPERS, Philadelphia.

Treatment, Neurosurgery

EFFECTS OF ORAL TOLSEROL ON SOME ASPECTS OF ELECTROSHOCK CONVULSIONS. FRANK D. GEER, Dis. Nerv. System **11**:27 (Jan.) 1950.

A trial of mephenesin (Tolserol; Myanesin) in electroshock therapy has seemed justified in view of the drug's reported peripheral curare-like qualities, ability to reduce rigidity, and anticonvulsant properties in animals. Thirteen patients received electroshocks without and with preliminary oral use of mephenesin in doses of 1 to 3.4 gm. one-half hour before treatment. It was found that with the drug a larger amount of current was required to induce a seizure and that in higher doses the tonic stage was shorter, though of equal or enhanced rigor. There was no significant alterations in the period of clonus; the time of apnea was only slightly decreased, and the blood pressure and pulse were essentially unchanged. It is concluded that mephenesin is of no demonstrable value in electroconvulsive therapy and is contraindicated because of its apparent action in making the tonic phase severer.

BEATON, Tucson, Ariz.

EXPERIENCES WITH ANTABUSE [DISULFIRAM] TREATMENT OF ALCOHOLISM IN A GENERAL HOSPITAL. A. E. BENNET, L. G. MCKEEVER, and R. E. TURK, J. Nerv. & Ment. Dis. **112**:393 (Nov.) 1950.

The authors treated 27 alcoholic patients of middle-class background who were in close contact with their families, both with intensive psychotherapy and with disulfiram (Antabuse). The patients were followed for three to nine months. Sixteen patients abstained from alcohol during this entire period. Four had one episode of alcoholism but subsequently continued to cooperate. Of the seven patients who returned to alcoholism, four had lack of family cooperation, and the others showed undesirable side-effects from the drug. One patient had an organic psychosis, which subsided after discontinuation of the treatment, and in two toxic hepatitis and gastrointestinal dysfunction, respectively, developed. All patients experienced some lassitude, often to the point of interference with normal functioning.

BERLIN, Mount Vernon, N. Y.

BENADRYL [DIPHENHYDRAMINE] IN THE TREATMENT OF PARKINSON'S DISEASE. M. T. MOORE, Neurology **1**:123 (March-April) 1951.

Fifty-two patients with various forms of Parkinson's disease were treated with diphenhydramine (Benadryl). The drug was administered orally and parenterally, alone and in conjunction with belladonna compounds. The patients in this series did not do well on oral administration of diphenhydramine alone. The most striking and beneficial results were obtained when the drug was used together with members of the atropine group. Eighty per cent of patients in this series showed improvement, and 20% did not. None of the patients was made worse. No alterations were observed in the hematologic findings after continued therapy. The only side-effect was that of drowsiness, which occurred in about 25% of the patients, but that was overcome with the use of amphetamine.

The results obtained in this study from the combined use of diphenhydramine and belladonna derivatives are superior to those which have been observed in the past with solanaceous drugs alone. Trihexyphenidyl (Artane) was found to be effective in treatment when used alone in approximately 15% of patients in this series. In about two-thirds of those patients in whom the use of diphenhydramine and scopolamine hydrobromide proved insufficiently beneficial, the addition of trihexyphenidyl yielded superior results.

Moore points out that each patient with Parkinson's disease requires experimentation with the drugs employed in this series, used as single agents and in various combinations, before the most satisfactory formula is achieved.

ALPERS, Philadelphia.

MEDICAL TREATMENT OF PSYCHOMOTOR EPILEPSY. J. K. MERLIS, Neurology **1**:245 (May-June) 1951.

Quantitative data on the drug treatment of psychomotor epilepsy are rare. The case series are small and are of questionable statistical validity. However, on the basis of available data, diphenylhydantoin (Dilantin), trimethadione (Tridione), methylphenylethylhydantoin (Mesantoin), and phenacemide (Phenurone) may be considered to be of some value in therapy. All these drugs have produced dangerous, often fatal, blood dyscrasias, the lowest incidence having occurred with diphenylhydantoin.

Merlis presents evidence to indicate that periodic blood counts are of little aid in reducing the morbidity or mortality of blood dyscrasias due to these drugs and do little more than provide the physician with a false sense of security. In terms of the morbidity of blood dyscrasia and other serious toxic phenomena, the safest of the antiepileptic drugs are phenobarbital and diphenylhydantoin. Available data indicate that diphenylhydantoin, alone or in combination with phenobarbital, is effective in a certain percentage of patients with psychomotor epilepsy. The most rational approach to drug therapy would appear to be the exploration of these drugs to the limit of their usefulness before using others considerably more dangerous. The other drugs should be used only after careful consideration, with the knowledge that occasional fatalities may be anticipated.

ALPERS, Philadelphia.

ANTICONVULSANT AND TOXIC EFFECTS OF ALPHA-PHENYL-BUTYRYL UREA. M. J. ORLOFF, P. E. FELDMAN, C. H. SHAIOVA, and C. C. PFIFFER, Neurology **1**:377 (Sept.-Oct.) 1951.

Alpha-phenylbutyryl urea, the ethyl analogue of phenacemide (phenurone®) and the aliphatic analogue of phenobarbital, was found to be a potent anticonvulsant against artificially induced convulsions in laboratory animals. Further, it was found to be chronically nontoxic in effective doses.

In a group of 10 institutionalized patients with severe epilepsy this drug appeared to be effective in controlling grand mal seizures. However, the drug produced severe toxic effects when doses necessary to bring about adequate control were given. Alpha-phenylbutyryl urea was not given an adequate trial in psychomotor epilepsy, but from the evidence now available it appears that the drug increases the frequency of psychomotor attacks. Alpha-phenylbutyryl urea was not tested in petit mal epilepsy. The authors state that the extreme toxicity of the drug at effective anticonvulsant dosage levels precludes its use as a therapeutic agent in the treatment of epilepsy.

ALPERS, Philadelphia.

HEADACHE: WITH SPECIAL REFERENCE TO THE EXCESSIVE USE OF ERGOTAMINE PREPARATIONS AND WITHDRAWAL EFFECTS. G. A. PETERS and B. T. HORTON, Proc. Staff Meet., Mayo Clin. **26**:153 (April 25) 1951.

Peters and Horton observed 19 patients with periodic headache who used excessive quantities of ergot preparations. Toxic reactions were encountered in 13. No frank migraine was observed. Several patients who were taking large quantities of ergotamine tartrate, some of whom had toxic symptoms, had no elevation of the blood pressure. There appeared to be an individual variation in the level of tolerance to the ergotamine preparation at which symptoms of toxicity would occur. Few toxic symptoms were observed from the use of dihydroergotamine (D.H.E. 45) alone.

Seven patients acquired such dependence on ergotamine tartrate that when use of the drug was discontinued daily headaches occurred; this suggested an ergotamine tartrate-withdrawal type of headache. Peters and Horton suggest that this may be likened to the rebound phenomenon observed in the nasal mucosa after the effect of vasoconstricting drugs has worn off, although there may be a psychogenic factor as well.

The clinician should thus be cautious in the administration of ergotamine preparations, instructing the patient to use the drug sparingly because (1) toxic symptoms may develop, (2) too much dependence on the drug may develop, and (3) withdrawal headaches may occur.

ALPERS, Philadelphia.

TREATMENT OF POSTLUMBAR PUNCTURE HEADACHE WITH DHE-45 (DIHYDROERGOTAMINE). W. G. CALDWELL, West. J. Surg. **58**:11 (Jan.) 1950.

Caldwell's study is limited to obstetrical patients delivered vaginally under low spinal anesthesia. Headache is the chief untoward reaction following spinal and saddle-block anesthesia. Rest in bed in the horizontal position is the best therapy, but in some cases considerable time must elapse before the headache disappears. Caldwell used dihydroergotamine methanesulfonate (DHE 45) in the treatment of postlumbar puncture headache. He studied it in preference to ergotamine tartrate, because there is evidence that it has the same degree of effectiveness as ergotamine tartrate but is considerably less toxic. Of 42 patients treated, 32 obtained complete relief; 7, no relief, and 3, minimal relief. The drug was administered in three ways: (1) intramuscularly, (2) intravenously, or (3) intravenously with the simultaneous intramuscular injection of one ampul (7½ grains, 0.5 gm.) of caffein and sodium benzoate. The third method proved to be the most efficacious. The only side-effects experienced were transient vertigo, lightheadedness, and slight nausea. None of these side-effects proved troublesome, and all subsided within 30 to 40 minutes.

J. A. M. A.

TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN. S. J. M. RUSSELL and P. MACARTHUR, Brit. M. J. **1**:192 (Jan. 24) 1953.

Russell and MacArthur present a follow-up report of results 49 to 68 months following treatment with streptomycin of 33 patients with proved meningitis. At the time of the report 12 patients were alive, of whom 9 were leading normal lives and 3 were grossly disabled; the remaining 21 had died, after periods ranging from two days to five years. Spinal block occurred in nine patients, of whom seven have died; and one of the two others still has a partial block. Intracranial calcification was noted in the roentgenograms of 10 of the 13 patients who lived long enough for it to develop. Of these, six are now well, two are disabled, and two have died. The meningitis recurred in nine children, only one of whom was alive and well at the time of the report. Two others were disabled, and the rest died as a result of the relapse.

ECHOLS, New Orleans.

VALUE OF STREPTOMYCIN IN SURGICAL TREATMENT OF INTRACRANIAL TUBERCULOMA. S. OBRADOR and P. URQUIZA, J. Neurol., Neurosurg. & Psychiat. **13**:66 (Feb.) 1950.

Surgical treatment of intracranial tuberculoma has been unsatisfactory in the past, as fatal tuberculous meningitis developed in most cases shortly after the operation. In Spain, according to Obrador and Urquiza, tuberculoma is still frequent. Tuberculomas represent, in the experience of these authors, nearly 10% of the brain tumors and other expanding lesions. The authors report observations on the first 10 of 16 patients with tuberculoma who had a sufficiently long follow-up period. Of four patients treated only surgically, one recovered from a supratentorial tuberculoma, two died of postoperative tuberculous meningitis, and one died of increased intracranial pressure. In another case streptomycin was not given intrathecally until after the operation; although the patient died several months later of generalized tuberculosis, the meninges were free from disease. In the next five patients of this series the tuberculomas were removed completely. The patients received streptomycin intramuscularly and intrathecally for two to three months afterward. The drug was given intramuscularly in daily doses of 1 gm. for 43 to 78 days. The intrathecal injections were given either by the intraventricular or the lumbar route for 35 to 60 days after the operation, in doses from 50 to 100 mg. daily during the first four weeks of treatment and afterward every other day. All the five patients who received postoperative streptomycin therapy have recovered and have remained well for periods of one to over one and a half years since operation. In four the tuberculoma was in the posterior fossa. These results demonstrate that streptomycin has changed the outlook in the surgical treatment of intracranial tuberculoma, and that it is capable of preventing the postoperative spread to the meninges.

J. A. M. A.

DIAGNOSIS AND TREATMENT OF BULBAR POLIOMYELITIS. W. HOWLETT KELLEHER, Lancet **1**:973 (May 5) 1951.

Kelleher reviews the diagnostic features of various types of bulbar poliomyelitis and discusses the chief aspects of treatment. He follows the classification of bulbar poliomyelitis suggested by the Minnesota Poliomyelitis Research Commission in 1947, although he states that, strictly speaking, it is applicable only to poliomyelitis with a lesion in the medulla oblongata. The classification includes the cranial nerve nuclei group, the respiratory center group, the circulatory center group, and the encephalitic group.

The cranial nerve nuclei group is divided into an upper subgroup, including the nuclei of the 3d, 4th, 5th, 6th, 7th, and 8th cranial nerves, and a lower subgroup, including the rest of the cranial nerves but concerned chiefly with the nucleus of the 10th nerve. Lesions of the upper subgroup commonly included disturbances of the fifth nerve, facial nerve paralysis, and vertigo and vomiting. Ocular signs were uncommon. In many of these cases the involvement was slight, and the author states that most of the patients partially recovered in due course.

The dangers of bulbar poliomyelitis are with lesions of the lower subgroup, particularly in cases of involvement of the 10th nerve nucleus, with resultant respiratory difficulty. The chief concern is with the accumulation of secretions, owing to neural dysfunction of the pharyngolaryngeal area, where aspiration of even small quantities of secretion into the larynx may set up reflex spasm and dangerous collapse.

Lesions of the respiratory center may be commoner than is suspected and may result in irregularities of depth and rhythm of respiration. Periods of apnea may occur, and the patient may be apprehensive and restless, symptoms which have been ascribed to hypoxia.

The author personally saw no patients with lesions of the circulatory center but describes the principal clinical features as a florid, dusky-red color, cherry-red lips, and a very rapid pulse, with varying, but usually low, blood pressure.

Symptoms of encephalitis are common in poliomyelitis and include apprehension, restlessness, irritability, twitching of facial muscles, tremors, and insomnia. Although the cause of these symptoms is not certain, the author seems to favor the theory of hypoxia of nerve cells rather than direct damage by the virus, and feels that critical effects of hypoxia on important areas, such as the respiratory and vasomotor centers, cannot be ignored.

The causes of anoxia in bulbar poliomyelitis (quite apart from that resulting from lesions of the cervical portion of the cord producing paralysis of respiratory muscles, and from interference with the proper functioning of vital autonomic centers in the medulla) are entirely mechanical or local. The most important defect of all is the accumulation of secretions in the pharynx, mainly from involvement of the 10th cranial nerve. Also important is paresis or paralysis of laryngeal abductors. Reflex laryngeal spasm, through irritation by food or fluid particles when glottic protection is defective, may be more important than is generally appreciated. The not uncommon complication of pneumonia and, particularly, atelectasis, will add to, or produce, hypoxia. Finally, there is the dreaded complication pulmonary edema.

The importance of recognizing the serious effects of lesions of the respiratory and cardiovascular centers in bulbar poliomyelitis is undoubted, for in a small proportion of cases it may be possible to save the patient. Recognition of the more local and mechanical defects, leading to defective oxygenation in bulbar poliomyelitis is, because of the claimed results for therapy, of much greater importance.

In reviewing treatment, the author discusses ascorbic acid and curare among the drugs used. He also considers nasal feedings but states that he fears them except in cases of the most suitable type.

The crux of the whole problem in the physical correction of the results of pharyngeal defects in bulbar poliomyelitis is how to keep the airway clear. There are at least two distinct aids: early postural drainage, assisted by aspiration, and tracheotomy. The author believes the poliomyelitis team should include an anesthetist and a laryngologist, who should be prepared to perform tracheotomy as a carefully planned measure of prevention, rather than of cure, of the dangerous sequelae of respiratory obstruction.

MADOW, Philadelphia.

EFFECTS OF INTRATHECAL TUBERCULIN AND STREPTOMYCIN IN TUBERCULOUS MENINGITIS: AN INTERIM REPORT. H. V. SMITH and R. L. VOLLUM, Lancet **2**:275 (Aug. 19) 1950.

When tuberculous meningitis is treated for a long time with intramuscular and intrathecal injections of streptomycin, between 50 and 60% of patients recover. But the mortality has not been further reduced, and in the individual case the prognosis remains uncertain.

The authors studied the cerebrospinal fluid during the first few weeks of streptomycin therapy and noted that the fluctuations in the cell count and protein level suggest that tuberculin is liberated into the cerebrospinal fluid.

In patients without meningitis but sensitized to tuberculoprotein, as shown by a positive reaction in the Mantoux test, an intrathecal injection of minute amounts of the purified protein derivative of tuberculin U. S. P. produces fever and vomiting and also a pleocytosis and rise in protein in the cerebrospinal fluid indistinguishable from the changes seen in patients with untreated tuberculous meningitis. Rather larger doses reproduce the changes seen in cells and protein when tuberculous meningitis is treated with streptomycin.

In certain cases of tuberculous meningitis in which streptomycin has failed to effect a cure, the cerebrospinal fluid becomes sterile, and fluctuations in the cells and protein disappear. In two such cases the intrathecal injections of purified protein derivative of tuberculin given when the patients were apparently moribund reproduced the rise in cells and protein seen typically during the first few weeks of streptomycin therapy. In both patients these injections were followed by a totally unexpected recovery, which appears to be complete over a year after treatment was first begun.

Intrathecal injections of purified protein derivative of tuberculin U. S. P. were given in a third case in which the full decerebrate state had developed. The illness was prolonged for six months, and a definite objective improvement was seen, though this never amounted to a useful recovery. At necropsy no exudate was seen macroscopically surrounding the brain stem.

In all three cases severe exudate must have been present and have resolved after the purified protein derivative of tuberculin was given. The authors suggest that the effects of tuberculin should be further explored now that any consequent spread of infection can be controlled by giving streptomycin at the same time.

Combined treatment with intrathecal injection of purified protein derivative of tuberculin and streptomycin has been begun by Smith and Vollum in seven other cases selected as having a bad prognosis. It is still too early to assess the results, but there has been only one death in the first three months of treatment. This compares favorably with the results on streptomycin alone.

ALPERS, Philadelphia.

BLOOD THERAPY IN NEUROLOGICAL DISEASES. H. TSCHABITSCHER and J. WALDSCHUTZ, Wien. klin. Wchnschr. **61**:171 (March 18) 1949.

Over 300 patients with multiple sclerosis were treated by the administration of human blood. The patients usually received 10 cc. of blood intramuscularly for 10 to 30 doses. The patients whose cases are reported were observed over a period of six months to three years. Approximately half the patients showed improvement during the treatment; one-fourth improved by the end of it. About two-thirds of the patients had febrile reactions, which occurred just as often after the first as after the second or third injection, and sometimes even at the end of the treatment. Recipients belonging to blood Type B had the fewest febrile reactions; most recipients of Type O had them. The recipients of any blood type had fewer febrile reactions when receiving Type AB or Type B blood, while Type O blood produced this reaction most frequently. Aside from transient increase in spasticity and tiredness, no untoward reaction was observed.

The authors believe that this type of therapy is effective because the patient receives in the blood injected not only antibodies already formed but also antigens, and therefore the procedure resembles active immunization. It is believed also that the injections produce nonspecific, polyvalent antibodies, among which may be found those which combat the as yet unknown virus of multiple sclerosis.

MASON, New York.

CURARE IN PROPHYLAXIS IN ELECTROSHOCK. P. FLORDH, Nord. med. **43**:250 (Feb. 10) 1950.

Flordh reports on the use of tubocurarine chloride in electroshock treatment of 131 patients. The dose was 0.15 mg. per kilogram of body weight, which gives moderate curarization. Ergographic examination was made to exclude myasthenia gravis. All patients received neostigmine intravenously. There were few side-effects, and these affected mainly the upper respiratory tract and could always be controlled by keeping the respiratory passages open and occasionally by supplying artificial respiration with the oxygen bag (Salvator). Curare is contraindicated in myasthenia gravis and in extreme restlessness. It may be given in all other types of cases but is especially recommended for men, for elderly patients, and for all patients with signs of skeletal disease and skeletal injury. X-ray examination of the thoracic portion of the spinal column was made before and after treatment in 90 patients. Comparison with 68 patients previously treated without curare and similarly examined showed a pronounced reduction in the frequency of fractures. With curare prophylaxis the indications for electroshock treatment can be extended to include cases in which the treatment was formerly contraindicated.

J. A. M. A.

TREATMENT OF NEUROSYPHILIS WITH HYPERTHERM. K. NØRGAARD, Nord. med. **43**:257, 1950.

Of 91 patients with neurosyphilis given hyperthermia-arsphenamine-bismuth treatment, 61 were followed up for six months to four years. The results showed 37 to be well or considerably improved, 14 slightly improved, and 10 not improved. Of the 32 with "active" spinal fluid, 23 were well or considerably improved, 8 somewhat improved, and 1 not improved. The Wassermann test disclosed a return to normal in 13 of the patients with active and 4 with inactive syphilis. Hyperthermia therapy is of great value in neurosyphilis, and, since it is associated with fewer risks and inconveniences than malaria treatment, it may eventually be adopted as the standard method, unless penicillin therapy alone is accepted as sufficient.

J. A. M. A.

Encephalography, Ventriculography and Roentgenography

CHONDROECTODERMAL DYSPLASIA. J. CAFFEY, Am. J. Roentgenol. **68**:875 (Dec.) 1952.

Caffey reports on the clinical and roentgenologic findings in three patients with chondroectodermal dysplasia. Ellis and van Creveld first described and named the syndrome in 1940. One of their patients had previously been described in 1933 by McIntosh. The same girl who has been described in the previous two articles is described again by Caffey. She is now 19 years of age. The other patients are an infant of 13 months and a child of 3 years.

All five of the recorded cases of chondroectodermal dysplasia have presented the following clinical features: hypoplasia of teeth and nails; shortening of the bones in the arms and legs; bilateral manual polydactylism and polymetacarpalism; synmetacarpalism; bilateral fusion of the capitate and hamate bones; changes in maturation of the ossification centers of the phalanges, and characteristic deformities in the proximal ends of the tibias, proximal ends of the ulnas, and distal ends of the radiuses. Other lesions which have been found in some of the cases, but not in all, are fusion of the upper lip and its gum, congenital malformation of the heart, alopecia, polymetatarsalism, polydactyly and syndactyly in the feet, dislocation of the heads of the radiuses, and retarded maturation of the manual sesamoid bones.

Caffey believes that chondroectodermal dysplasia is a distinct syndrome made up of several characteristic components, which serve to differentiate it without question from other congenital dysplasias and from other forms of dwarfism. Dwarfism in this syndrome is due almost exclusively to shortening of the legs.

WEILAND, Grove City, Pa.

MYELOGRAPHIC DEMONSTRATION OF SPINAL CORD METASTASES FROM PRIMARY BRAIN TUMORS. E. H. WOOD; J. M. TAVERAS, AND J. L. POOL, Am. J. Roentgenol. **69**:221 (Feb.) 1953.

Studies by pathologists and surgeons have demonstrated that metastasis of primary brain tumors to other parts of the central nervous system by way of the cerebrospinal fluid is a relatively common occurrence. Myelography may be used for detecting spinal metastases from primary brain tumors and for determining the effect of x-ray therapy upon such lesions. The

commonest type of metastasis from a glioma is a group of discrete nodular implants on the surface of the spinal cord and its nerve roots. Such metastases are usually histologically similar to the parent tumor. A less common form of metastasis from glioma is diffuse involvement of the meninges with metastatic tumors. Fibrosis often causes this type of metastasis to have a slightly different appearance than the parent tumor. Symptoms produced by the metastases vary with the size and location of the lesions. Pleocytosis and increase of protein in the cerebrospinal fluid are the general rule, and neoplastic cells often can be found in centrifuged specimens. Usually no abnormalities can be demonstrated in plain roentgenograms of the spine.

The authors report on four patients with primary brain tumors in whom metastases to the spinal cord were demonstrated by myelograms. Two patients had cerebral glioblastoma multiforme. The other two had cerebellar tumors: one, medulloblastoma, and one, hemangioblastoma. In all four patients the myelograms disclosed multiple filling defects in the outline of the subarachnoid space. The defects were rounded in outline and ranged from less than 1 mm. to 2 cm. in diameter. In one patient a partial obstruction was found in the thoracic region, and in another a complete obstruction was found low in the lumbar region of the spinal canal. Myelographic studies were performed on two patients before and after deep x-ray therapy. After irradiation of the spine of one patient, with glioblastoma multiforme with spinal metastasis, the myelogram (second) demonstrated that some of the lesions had disappeared and that others had become smaller. In the second patient, metastatic nodules from a cerebellar hemangioblastoma were reduced slightly by irradiation of the spine. The use of 9 to 12 cc. of ethyl iodophenylundecylate (Pantopaque) is recommended for these studies, since most of the metastases are on the dorsal surface of the cord, and lesions in this location cannot be demonstrated well with small amounts of the opaque material.

WEILAND, Grove City, Pa.

REPORT OF A CASE OF EOSINOPHILIC GRANULOMA OF BONE WITH ROENTGENOGRAPHIC DEMONSTRATION OF A SEQUESTRUM. R. G. WILSON, D. W. MINTEER, and J. D. HAYES, Am. J. Roentgenol. **69**:936 (June) 1953.

Wilson, Minteer, and Hayes report the case of an 18-year-old boy who was admitted to the hospital with a swollen, tender area over the left frontal bone. Roentgenograms of the skull revealed a circular radiolucent area, about 2.5 cm. in diameter, involving both tables of the frontal bone. In the center of the defect was a large sequestrum about 2 cm. in diameter. The margins of the radiolucent lesion were sharp and regular, but the margins of the sequestrum were poorly defined.

Histologic study of the tissue removed surgically showed the lesion to be an eosinophilic granuloma containing a large sequestrum of bone. This diagnosis was confirmed when the slides were reviewed at the Armed Forces Institute of Pathology. The authors reviewed 200 cases of eosinophilic granuloma reported in the medical literature and found no reference to roentgenographic demonstration of sequestration in any of the cases.

WEILAND, Grove City, Pa.

News and Comment

RORSCHACH TEST WORKSHOP SEMINARS, UNIVERSITY OF CHICAGO

The Department of Psychology, University of Chicago, announces two workshop seminars in the Rorschach test, July 6-10 and 12-16, 1954 (inclusive). These will be conducted by Dr. S. J. Beck.

Workshop I, Basic Processes, will provide a grounding in fundamentals. The procedure in obtaining the test record will be discussed. Representative responses will be illustrated and their scoring clarified, with especial reference to their interrelations in shaping the whole personality structure. Introduction to interpretation.

Workshop II, Advanced Clinical Interpretation, will consider the ego, anxiety, and the individual's psychological reserves as treatment potential. The cases will illustrate "schizogenic" conditions in children and some milder disorders in children and adults. They will exemplify anxiety of "central" (inner) source, as well as of peripheral stimulation. In exploring for reserves, both structure and content will be scrutinized.

Workshop I may be taken by students at, or ready for, the intern level. Admission to Workshop II is limited to psychologists and psychiatrists in clinical positions or practice. Each seminar will meet at the university for five days, with two sessions each day, two hours per session.

For all information as to admission, fees, or academic credit arrangements, write to the Executive Secretary, Department of Psychology, The University of Chicago, Chicago 37.

FOURTH ANNUAL INSTITUTE IN PSYCHIATRY AND NEUROLOGY

The Veterans Administration Hospital, Lyons, N. J., the New Jersey Neuropsychiatric Association, and the New Jersey District Branch of the American Psychiatric Association will hold the Fourth Annual Institute in Psychiatry and Neurology at the Veterans Administration Hospital, Lyons, April 21, 1954; moderators, Dr. Daniel Blain, Dr. Stephen P. Jewett, and Dr. Harvey J. Tompkins.

The official program follows:

Emotional Deprivation in Infancy and Its Implications in Child Psychiatry	Dr. Lauretta Bender
The Administrator's Place in Psychiatry	Dr. Arthur P. Noyes
Sexual Psychopathology and Crime	Dr. Benjamin Karpman
The Origin of Human Movement	Dr. Temple Fay

Clinics Exhibits Scientific movie

7:00 p. m.: Dinner

After the dinner, Dr. Leo Bartemeier will speak on Failures in Psychotherapy.

Registration fee of $1.00 will include a copy of the *Proceedings* of the Institute (military personnel and full-time Veterans Administration personnel exempt). Additional information may be obtained from Dr. Crawford N. Baganz, manager.

ASSOCIATION FOR THE ADVANCEMENT OF PSYCHOANALYSIS, INC.

On March 24, 1954, the Association for the Advancement of Psychoanalysis sponsored the annual Karen Horney Lecture at the New York Academy of Medicine at 8:30 p. m., preceded by a dinner in the President's Gallery of the New York Academy of Medicine.

Dr. John C. Whitehorn, Professor of Psychiatry, spoke on "The Scope of Motivation in Psychopathology and Psychotherapy."

TWENTY-SIXTH NATIONAL CONGRESS OF PSYCHIATRY, VARESE, ITALY

The 26th Congress of the Italian Association of Psychiatry will be held at the Neuropsychiatric Hospital, Varese, Italy, May 6-9, 1954.

The president of the organizing committee is Prof. A. M. Fiamberti, and the secretary-general is Dr. E. Balduzzi.

The titles of the reports (with the names of the reporters) are as follows:

I. Recent Discoveries in Infantile Encephalopathy (Phenylpyruvic Oligophrenia by Rh Factor, Maternal Rubella, Thesaurismosis, etc.), Prof. L. Bini, Rome; Prof. G. Campailla, Ferrare; Prof. G. Fasanaro, Naples

II. New Perspectives in Quantitative Differentiation Between Psychasthenia and Schizophrenia, Prof. G. Gastaldi, Modène; Prof. G. Padovani, Turin; Dr. G. LoCascio, Rome

All communications concerning neuropsychiatry will be accepted. The participation of foreign colleagues is desired.

The conference will include excursions and cultural activities, the program for which will be sent to all participants. The fee has been set at 3,000 lire ($5).

Address all correspondence to Presidency of XXVIth National Congress of the Italian Society of Psychiatry, Ospedale, Neuro-Psichiatrico, Varese, Italy.

FIRST INTERNATIONAL CONGRESS ON GROUP PSYCHOTHERAPY, TORONTO, CANADA

The international committee on group psychotherapy has organized the First International Congress on Group Psychotherapy to be held in Toronto, Canada, Aug. 12 and 20, 1954, in connection with the Fifth International Congress on Mental Health. The conference will promote the exchange of information and intensify personal contact between workers in mental health and allied professions throughout the world.

A series of meetings has been arranged. Papers and symposia will deal with group psychotherapy and group studies in the areas of family relations and the national and international communities.

Therapeutic work with children and parents, adolescents and the aged addicts and delinquents will be presented. The use of groups in education, industry, and government and the work with different ethnic groups are among the subjects with which panel discussions will deal. There will also be discussion groups dealing with various aspects of group psychotherapy and group studies during the week of Aug. 16.

Representatives of 23 nations participate in the organization of the Congress. Wilfred C. Hulse and Wellman J. Warner are chairmen; J. L. Moreno and S. R. Slavson are consulting chairmen.

For full details write to International Congress on Group Psychotherapy, Room 916, 1790 Broadway, New York 19.

RESIDENCIES IN PSYCHIATRY, VETERANS ADMINISTRATION HOSPITAL, LYONS, N. J.

The Veterans Administration Hospital, Lyons, N. J., has available residencies in psychiatry for a one- to three-year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences, and seminars under the direction of the Department of Psychiatry, New York Medical College, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers, as well as an annual institute at the hospital. Training may commence at any time.